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BIOASSAY OF m-CRESIDINE FOR POSSIBLE CARCINOGENICITY

CAS No. 102-50-1

NCI-CG-TR-105

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
National Institutes of Health

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

National Institutes of Health

REPORT ON BIOASSAY OF M-CRESIDINE FOR POSSIBLE CARCINOGENICITY

Availability

m-Cresidine (CAS 102-50-1) has been tested for cancer-causing activity with rats and mice in the Bioassay Program, Division of Cancer Cause and Prevention, National Cancer Institute. A report is available to the public.

Summary: A bioassay of technical-grade m-cresidine for possible carcinogenicity was conducted using Fischer 344 rats and B6C3F1 mice. Applications of the chemical include use as an intermediate in the manufacture of dyes. m-Cresidine in corn oil was administered by gavage five days a week at either of two dosages, to groups of 50 male and 49 or 50 female animals of each species.

Under the conditions of this bioassay, m-cresidine was carcinogenic to Fischer 344 rats, causing papillary transitional-cell carcinomas of the urinary bladder in both sexes. No convincing evidence was provided for carcinogenicity in female B6C3F1 mice. Poor survival of male B6C3F1 mice receiving m-cresidine precluded evaluation of the possible carcinogenicity of the compound in these animals.

Single copies of the report are available from the Office of Cancer Communications, National Cancer Institute, Building 31, Room 10A21, National Institutes of Health, Bethesda, Maryland 20014.

Dated: September 29, 1978

Director
National Institutes of Health

(Catalogue of Federal Domestic Assistance Program Number 13.393, Cancer Cause and Prevention Research)

HEW NEWS

U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

FOR RELEASE IN A.M. PAPERS
Friday, September 29, 1978

National Institutes of Health
Office of Cancer Communications
(301) 496-6641

Availability of a report on animal tests of m-cresidine for cancer-causing activity (carcinogenicity) was announced by HEW's National Cancer Institute in today's Federal Register.

m-Cresidine, an intermediate in the manufacture of dyes, was given by stomach tube to rats and mice for periods between 53 and 77 weeks. According to a summary of the report included in the announcement, m-cresidine caused bladder cancer in male and female rats. No evidence of carcinogenicity was found in female mice, but poor survival in male mice precluded evaluation of the compound in these animals.

The tests are part of the Institute's Bioassay Program. Copies of the report, Bioassay of m-Cresidine for Possible Carcinogenicity, are available from the Office of Cancer Communications, National Cancer Institute, Bethesda, Maryland 20014.

# # # #

BIOASSAY OF
m-CRESIDINE
FOR POSSIBLE CARCINOGENICITY

Carcinogenesis Testing Program
Division of Cancer Cause and Prevention
National Cancer Institute
National Institutes of Health
Bethesda, Maryland 20014

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
National Institutes of Health

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1998

REPORT ON THE BIOASSAY OF m-CRESIDINE
FOR POSSIBLE CARCINOGENICITY

CARCINOGENESIS TESTING PROGRAM
DIVISION OF CANCER CAUSE AND PREVENTION
NATIONAL CANCER INSTITUTE, NATIONAL INSTITUTES OF HEALTH

FOREWORD: This report presents the results of the bioassay of m-cresidine conducted for the Carcinogenesis Testing Program, Division of Cancer Cause and Prevention, National Cancer Institute (NCI), National Institutes of Health, Bethesda, Maryland. This is one of a series of experiments designed to determine whether selected chemicals have the capacity to produce cancer in animals. Negative results, in which the test animals do not have a significantly greater incidence of cancer than control animals, do not necessarily mean the test chemical is not a carcinogen because the experiments are conducted under a limited set of circumstances. Positive results demonstrate that the test chemical is carcinogenic for animals under the conditions of the test and indicate a potential risk to man. The actual determination of the risk to man from animal carcinogens requires a wider analysis.

CONTRIBUTORS: This bioassay of m-cresidine was conducted by Mason Research Institute, Worcester, Massachusetts, initially under direct contract to the NCI and currently under a subcontract to Tracor Jitco, Inc., prime contractor for the NCI Carcinogenesis Testing Program.

The experimental design was determined by the NCI Project Officers, Dr. J. H. Weisburger (1,2) and Dr. E. K. Weisburger (1). The principal investigators for the contract were Dr. E. Smith (3) and Dr. A. Handler (3). Animal treatment and observation were supervised by Mr. G. Wade (3) and Ms. E. Zepp (3). Chemical analysis was performed by Midwest Research Institute (4) and the analytical results were reviewed by Dr. N. Zimmerman (5).

Histopathologic examinations were performed by Dr. R. W. Fleischman (3), Dr. D. W. Hayden (3), Dr. A. S. Krishna Murthy (3), Dr. A. Russfield (3), Dr. D. S. Wyand (3), and Dr. Yoon (3) at the Mason Research Institute, and the diagnoses included in this report represent the interpretation of these pathologists. Histopathology findings and reports were reviewed by Dr. R. L. Schueler (6).

Compilation of individual animal survival, pathology, and summary tables was performed by EG&G Mason Research Institute (7); the statistical analysis was performed by Mr. W. W. Belew (5) and Dr. J. R. Joiner (6) using methods selected for the Bioassay Program by Dr. J. J. Gart (8).

This report was prepared at METREK, a Division of The MITRE Corporation (5) under the direction of the NCI. Those responsible for this report at METREK are the project coordinator, Dr. L. W. Thomas (5), the task leader, Dr. M. R. Kornreich (5), the senior biologist, Ms. P. Walker (5) and the technical editor, Ms. P. A. Miller (5). The final report was reviewed by members of the participating organizations.

The statistical analysis was reviewed by members of the Mathematical Statistics and Applied Mathematics Section of the NCI: Dr. J. J. Gart (8), Mr. J. Nam (8), Dr. H. M. Pettigrew (8), and Dr. R. E. Tarone (8).

The following other scientists at the National Cancer Institute were responsible for evaluating the bioassay experiment, interpreting the results, and reporting the findings: Dr. K. C. Chu (1), Dr. C. Cueto, Jr. (1), Dr. J. F. Douglas (1), Dr. D. G. Goodman (1), Dr. R. A. Griesemer (1), Dr. H. A. Milman (1), Dr. T. W. Orme (1), Dr. R. A. Squire (1,9), Dr. J. M. Ward (1), and Dr. C. E. Whitmire (1).

---

1. Carcinogenesis Testing Program, Division of Cancer Cause and Prevention, National Cancer Institute, National Institutes of Health, Bethesda, Maryland.

2. Now with the Naylor Dana Institute for Disease Prevention, American Health Foundation, Hammon House Road, Valhalla, New York.

3. Mason Research Institute, 57 Union Street, Worcester, Massachusetts.

4. Midwest Research Institute, 425 Volker Boulevard, Kansas City, Missouri.

5. The MITRE Corporation, METREK Division, 1820 Dolley Madison Boulevard, McLean, Virginia.

6. Tracor Jitco, Inc., 1776 East Jefferson Street, Rockville, Maryland.

7. EG&G Mason Research Institute, 1530 East Jefferson Street, Rockville, Maryland.

8. Mathematical Statistics and Applied Mathematics Section, Biometry Branch, Field Studies and Statistics Program, Division of Cancer Cause and Prevention, National Cancer Institute, National Institutes of Health, Bethesda, Maryland.

9. Now with the Division of Comparative Medicine, Johns Hopkins University, School of Medicine, Traylor Building, Baltimore, Maryland.

SUMMARY

A bioassay of technical-grade m-cresidine for possible carcinogenicity was conducted using Fischer 344 rats and B6C3F1 mice. m-Cresidine in corn oil was administered by gavage five days a week at either of two dosages, to groups of 50 male and 49 or 50 female animals of each species. The dosages used in the chronic bioassay for low and high dose rats were 0.08 and 0.16 gm/kg/day, respectively. The time-weighted average dosages used for low and high dose mice were 0.06 and 0.11 gm/kg/day, respectively. After a 77-week dosing period observation of rats continued for an additional 32 to 33 weeks. After a 53-week dosing period, observation of mice continued for an additional observation period of up to 41 weeks. For each species, 50 animals of each sex were placed on test as untreated controls and 25 animals of each sex were placed on test as vehicle controls.

The urinary bladder and the kidney were the target organs of m-cresidine toxicity in male and female rats. Papillary transitional-cell carcinomas of the urinary bladder occurred in 0/45 low dose males, 5/44 (11 percent) high dose males, 1/46 (2 percent) low dose females, and 2/44 (5 percent) high dose females but did not occur in any untreated control or vehicle control rats. Although the incidences in each dosed rat group were not statistically significant when compared to vehicle controls, comparison with historical controls indicates that these bladder carcinomas are rare and are, therefore, considered to be compound-related in both sexes.

Among mice, dose-related nonneoplastic lesions were observed at higher incidences for males than females in the kidneys, spleen and thymus. Dose-related toxic effects were also observed in the testes of male mice. No neoplasms occurred in male mice at statistically significant incidences.

Under the conditions of this bioassay, m-cresidine was carcinogenic to Fischer 344 rats, causing papillary transitional-cell carcinomas of the urinary bladder in both sexes. No convincing evidence was provided for carcinogenicity in female B6C3F1 mice. Poor survival of male B6C3F1 mice receiving m-cresidine precluded evaluation of the possible carcinogenicity of the compound in these animals.

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I. INTRODUCTION

m-Cresidine (NCI No. C02993), an aromatic amine and dyestuff intermediate, was selected for bioassay by the National Cancer Institute because of the high incidence of bladder cancer associated with exposure to aromatic amines and several other classes of chemicals among workers in the dye manufacturing industry (Wynder et al., 1963).

The Chemical Abstracts Service (CAS) Ninth Collective Index (1977) name for this compound is 4-methoxy-2-methylbenzenamine.* It is also called 4-methoxy-2-methylaniline and 2-methyl-p-anisidine.

m-Cresidine is used as an intermediate for the synthesis of C.I. (Colour Index) Azoic Diazo Coupling Component 24 (C.I. 37540) (Society of Dyers and Colourists, 1956).

Specific production figures for m-cresidine are not available; however, this compound does not appear to be produced commercially in the United States in quantities greater than 1000 pounds or $1000 in value annually (Stanford Research Institute, 1977).

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*The CAS registry number is 102-50-1.

II. MATERIALS AND METHODS

A. Chemicals

Technical-grade m-cresidine (2-methyl-p-anisidine) was purchased by the NCI for Mason Research Institute from Carroll Products, Wood River Junction, Rhode Island and chemical analysis was performed by Midwest Research Institute, Kansas City, Missouri. Thin-layer chromatography (TLC) was performed utilizing two solvent systems (chloroform and benzene:ethyl acetate), and each plate was visualized with ultraviolet light and furfural. TLC results indicated the presence of one impurity. Differences between results of the experimental elemental analysis and those expected on a theoretical basis suggested impurities. Titration of the amino group gave a result which was 98 percent of the theoretical. This does not necessarily mean that the test chemical was 98 percent pure m-cresidine as similar amino compounds may have been present as contaminants. Vapor-phase chromatography indicated the presence of three impurities, one of higher motility and two of lower motility than the major compound. Infrared analysis was consistent with that reported in the literature (Sadtler Standard Spectra, a). Nuclear magnetic resonance analysis was consistent with the structure of the compound (Sadtler Standard Spectra, b). Ultraviolet analyses showed two λ_{max} at 233 and 296 nm with respective molar extinction coefficients of 8300 and 2600. Values reported in the literature (Sadtler Standard Spectra, c) are λ_{max} = 255.5 and 296 with respective ϵ values of 8031 and 2740. These values suggest that the purity of the compound was approximately 96 percent.

Throughout this report the term m-cresidine is used to represent this technical-grade material.

B. Dosage Preparation

Fresh solutions of m-cresidine in shelf-grade Mazola® corn oil (Best Foods, Inc., Englewood Cliffs, New Jersey) were prepared weekly, sealed, and stored in dark vials at 4°C. The solutions were prepared on a weight basis.

C. Animals

Two animal species, rats and mice, were used in the carcinogenicity bioassay. Fischer 344 rats and B6C3F1 mice were obtained through contracts with the Division of Cancer Treatment, National Cancer Institute. Animals of both species were supplied by Charles River Breeding Laboratories, Wilmington, Massachusetts. Treated and control animals for both species were received in separate shipments.

Upon arrival, a sample of animals was sacrificed and examined for parasites and other visible signs of disease. The remaining animals were quarantined for 2 weeks prior to initiation of test. Animals were assigned to groups and distributed among cages so that average body weight per cage was approximately equal for a given sex and species.

D. Animal Maintenance

All animals were housed by species in rooms having a temperature range of 23° to 34°C. Incoming air was filtered through Tri-Dek®

15/40 denier Dacron® filters (Tri-Dim Filter Corp., Hawthorne, New Jersey) providing six changes of room air per hour. Fluorescent lighting was provided on a 12-hour-daily cycle.

Rats were housed five per cage by sex. During quarantine and for the first 16 months of study, rats were housed in galvanized-steel wire-mesh cages (Fenco Cage Products, Boston, Massachusetts) suspended over newspapers. Newspapers under cages were replaced daily, and cages and racks washed weekly. For the remainder of the study, all rats were housed in suspended polycarbonate cages (Lab Products, Inc., Garfield, New Jersey) equipped with disposable nonwoven fiber filter sheets. Clean cages and bedding were provided twice weekly. SAN-I-CEL® corncob bedding (Paxton Processing Company, Paxton, Illinois) was used during the first 6 months that rats were housed in polycarbonate cages. Aspen hardwood chip bedding (American Excelsior Company, Baltimore, Maryland) was used for the remainder of the study. Stainless steel cage racks (Fenco Cage Products) were cleaned once every 2 weeks, and disposable filters were replaced at that time.

Mice were housed by sex in polycarbonate cages fitted with perforated stainless steel lids (Lab Products, Inc.). Nonwoven fiber filter bonnets were used over cage lids. All female mice and treated male mice were housed ten per cage for the first 12 months and five per cage thereafter, while male control mice were housed ten per cage for the first 13 months and five per cage thereafter. Clean cages, lids, and bedding were provided three times per week when cage populations were ten and twice per week when cage populations were five. Ab-sorb-dri® hardwood chip bedding (Wilner Wood Products Company, Norway, Maine) was used for the treated and control mice for the first 3 and 4 months of the study, respectively. SAN-I-CEL® was then used for the next 12 months, after which a second corncob bedding (Bed-o-Cobs®, The Andersons Cob Division, Maumee, Ohio) was used for 8 months. Aspen bedding was then used until the end of the study. Reusable filter bonnets and pipe racks were sanitized every 2 weeks throughout the study.

Water was available *ad libitum* from 250 ml water bottles equipped with rubber stoppers and stainless steel sipper tubes. Bottles were replaced twice weekly and, for rats only, water was supplied as needed between changes.

During quarantine and the period of compound administration, all animals were supplied with Wayne Lab-Blox® meal (Allied Mills, Inc., Chicago, Illinois) *ad libitum*. Rats and mice were fed from Alpine® aluminum feed cups (Curtin Matheson Scientific, Inc., Woburn, Massachusetts) for the first 13 and 16 months of study, respectively. For the remainder of the study, rats and mice were fed from stainless steel gangstyle food hoppers (Scientific Cages, Inc., Bryan, Texas). During the observation period after compound administration, rats were fed Wayne Lab-Blox® pellets on the cage floor. Mice were fed pellets from wire bar lids which replaced the perforated cage lids during this period. Food hoppers of all types were changed on the same schedule as were cages. Food was replenished daily in Alpine® feed cups.

Rats dosed with m-cresidine were housed in the same room with their vehicle controls, and with other rats receiving diets containing* 2,5-dithiobiurea (142-46-1); fenaminosulf (140-56-7); and cupferron (135-20-6).

Mice dosed with m-cresidine were housed in a room where other mice were receiving diets containing 1,5-naphthalenediamine (2243-62-1); N-(1-naphthyl)ethylenediamine dihydrochloride (1465-25-4); and 1H-benzotriazole (95-14-7). Control mice were in a room with other mice receiving diets containing 2,5-dithiobiurea (142-46-1); cupferron (135-20-6); 4-chloro-o-phenylenediamine (95-83-0); o-anisidine hydrochloride (134-29-0); fenaminosulf (140-56-7); and p-anisidine hydrochloride (20265-97-8).

E. Gastric Intubation

Intubation was performed for five consecutive days per week on a gm/kg body weight basis utilizing the most recently observed group mean body weight as a guide for determining the dose. Mean body weights for each group were recorded at weekly intervals for the first 10 weeks and at monthly intervals thereafter. All animals of one sex within a treated group received the same dose. Animals were gavaged with test solutions under a hood to minimize extraneous exposure of other animals and laboratory personnel to the chemical.

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*CAS registry numbers are given in parentheses.

F. Selection of Initial Dose Levels

In order to establish the maximum tolerated concentrations of m-cresidine for administration to treated animals in the chronic studies, subchronic toxicity tests were conducted with both rats and mice. Animals of each species were distributed among six groups, each consisting of five males and five females. m-Cresidine, dissolved in corn oil, was introduced by gavage to five of the six rat groups at dosages of 0.02, 0.04, 0.08, 0.15, and 0.3 gm/kg/day and five of six mouse groups at dosages of 0.04, 0.08, 0.15, 0.3, and 0.6 gm/kg/day. The sixth group of each species served as a control group, receiving only the corn oil. Intubation was performed 5 days per week for a period of 7 weeks, followed by a 1-week observation period during which all animals were fed the untreated basal diet.

The highest dosage causing no deaths, no compound-related gross abnormalities, and no mean body weight depression in excess of 15 percent relative to controls was selected as the high concentration utilized for the rat and mouse chronic bioassays.

The only death reported among treated rats was one female receiving 0.15 gm/kg/day. Mean body weight depression was 26.5, 4.5, and 3.6 percent, respectively, in males treated with 0.3, 0.15, and 0.08 gm/kg/day. In females mean body weight depression, which occurred only in the group receiving 0.3 gm/kg/day, was 6.5 percent. The initial high dose selected for the chronic bioassay in rats was 0.16 gm/kg/day for both males and females.

Deaths occurred in male mice treated with m-cresidine at a dosage of 0.3 gm/kg/day or more and in female mice treated with 0.08 gm/kg/day or more. Mean body weight depression was 8.4 percent in males treated with 0.3 gm/kg/day, the only group of males experiencing mean body weight depression, and 18.4, 11.1, and 13.4 percent in females treated with 0.6, 0.3, and 0.15 gm/kg/day, respectively. The initial high dose selected for the chronic bioassay in mice was 0.16 gm/kg/day for both males and females.

G. Experimental Design

The experimental design parameters for the chronic study (species, sex, group size, actual dosages administered, duration of treated and untreated observation periods, and the time-weighted average dosages) are summarized in Tables 1 and 2.

The treated and vehicle control rats were approximately 6 weeks old when the first dose was administered and at that time untreated control rats were approximately 10 weeks old. The dosages of m-cresidine administered to rats were 0.16 and 0.08 gm/kg/day; throughout this report, the rats receiving the former dosage are referred to as the high dose rat groups and the rats receiving the latter dosage are referred to as the low dose rat groups. These levels were maintained throughout the 77 weeks of compound administration. An observation period of up to 33 weeks followed.

All mice were approximately 6 weeks old when the first dose was administered. The initial dosages of m-cresidine administered to

TABLE 1

DESIGN SUMMARY FOR FISCHER 344 RATS m-CRESIDINE GAVAGE EXPERIMENT

	INITIAL GROUP SIZE	m-CRESIDINE DOSAGE[a]	OBSERVATION PERIOD	
			TREATED (WEEKS)	UNTREATED (WEEKS)
MALE				
UNTREATED CONTROL	50	0	0	110
VEHICLE CONTROL	25	0	0	110
LOW DOSE	50	0.08	77	
		0		32
HIGH DOSE	50	0.16	77	
		0		33
FEMALE				
UNTREATED CONTROL	50	0	0	110
VEHICLE CONTROL	25	0	0	110
LOW DOSE	49	0.08	77	
		0		32
HIGH DOSE	50	0.16	77	
		0		33

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[a] Dosages, given in gm/kg body weight, were administered by gavage 5 consecutive days per week.

TABLE 2

DESIGN SUMMARY FOR B6C3F1 MICE
m-CRESIDINE GAVAGE EXPERIMENT

	INITIAL GROUP SIZE	m-CRESIDINE DOSAGE[a]	OBSERVATION PERIOD TREATED (WEEKS)	OBSERVATION PERIOD UNTREATED (WEEKS)	TIME-WEIGHTED AVERAGE DOSAGE[b]
MALE					
UNTREATED CONTROL	50	0	0	98	0
VEHICLE CONTROL	25	0	0	95	0
LOW DOSE	50	0.08	32		0.06
		0.02	21		
		0		40	
HIGH DOSE	50	0.16	32		0.11
		0.04	21		
		0		25	
FEMALE					
UNTREATED CONTROL	50	0	0	98	0
VEHICLE CONTROL	25	0	0	95	0
LOW DOSE	50	0.08	32		0.06
		0.02	21		
		0		41	
HIGH DOSE	50	0.16	32		0.11
		0.04	21		
		0		41	

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[a] Dosages, given in gm/kg body weight, were administered by gavage 5 consecutive days per week.

[b] Time-weighted average dosage = $\frac{\Sigma(\text{dosage X weeks received})}{\Sigma(\text{weeks receiving chemical})}$

mice were 0.16 and 0.08 gm/kg/day; throughout this report, the mice initially receiving the former dosage are referred to as the high dose mouse groups and the mice initially receiving the latter dosage are referred to as the low dose mouse groups. After 32 weeks the doses were reduced to 0.04 and 0.02 gm/kg/day for the high and low dose mice, respectively. These doses were maintained for the remainder of the period of dose administration, which was only 21 weeks. The early cessation of chemical administration (i.e., after week 53) was in response to excessive mortality among treated mice. An observation period of up to 41 weeks followed.

H. Clinical and Histopathologic Examinations

Animals were weighed immediately prior to initiation of the experiment. Body weights were recorded twice weekly for the first 12 weeks of the study and at monthly intervals thereafter. From the first day, all animals were inspected twice daily for mortality. Food consumption, for two cages from each group, was monitored for seven consecutive days once a month for the first nine months of the bioassay and for three consecutive days each month thereafter. The presence of tissue masses and lesions was determined by monthly observation and palpation of each animal.

A necropsy was performed on each animal regardless of whether it died, was killed when moribund, or was sacrificed at the end of the bioassay. The animals were euthanized by carbon dioxide inhalation, and were immediately necropsied. The histopathologic examination consisted of gross and microscopic examination of major tissues, organs, or gross lesions taken from sacrificed animals and, whenever possible, from animals found dead.

Slides were prepared from the following tissues: skin, subcutaneous tissue, lungs and bronchi, trachea, bone marrow, spleen, lymph nodes, thymus, heart, salivary gland, liver, gallbladder (mice), pancreas, esophagus, stomach, small intestine, large intestine, kidney, urinary bladder, pituitary, adrenal, thyroid, parathyroid, brain, testis, prostate, uterus, mammary gland, and ovary.

Tissues for which slides were prepared were preserved in 10 percent buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin prior to microscopic examination. An occasional section was subjected to special staining techniques for more definitive diagnosis.

A few tissues were not examined for some animals, particularly for those that died early. Also, some animals were missing, cannibalized, or judged to be in such an advanced state of autolysis as to preclude histopathologic interpretation. Thus, the number of animals for which particular organs, tissues, or lesions were examined microscopically varies and does not necessarily represent the number of animals that were placed on experiment in each group.

I. Data Recording and Statistical Analyses

Pertinent data on this experiment have been recorded in an automatic data processing system, the Carcinogenesis Bioassay Data System

(Linhart et al., 1974). The data elements include descriptive information on the chemicals, animals, experimental design, clinical observations, survival, body weight, and individual pathologic results, as recommended by the International Union Against Cancer (Berenblum, 1969). Data tables were generated for verification of data transcription and for statistical review.

These data were analyzed using the statistical techniques described in this section. Those analyses of the experimental results that bear on the possibility of carcinogenicity are discussed in the statistical narrative sections.

Probabilities of survival were estimated by the product-limit procedure of Kaplan and Meier (1958) and are presented in this report in the form of graphs. Animals were statistically censored as of the time that they died of other than natural causes or were found to be missing; animals dying from natural causes were not statistically censored. Statistical analyses for a possible dose-related effect on survival used the method of Cox (1972) when testing two groups for equality and used Tarone's (1975) extensions of Cox's methods when testing a dose-related trend. One-tailed P-values have been reported for all tests except the departure from linearity test, which is only reported when its two-tailed P-value is less than 0.05.

The incidence of neoplastic or nonneoplastic lesions has been given as the ratio of the number of animals bearing such lesions at a specific anatomic site (numerator) to the number of animals in which that site was examined (denominator). In most instances, the denominators included only those animals for which that site was examined histologically. However, when macroscopic examination was required to detect lesions prior to histologic sampling (e.g., skin or mammary tumors), or when lesions could have appeared at multiple sites (e.g., lymphomas), the denominators consist of the numbers of animals necropsied.

The purpose of the statistical analyses of tumor incidence is to determine whether animals receiving the test chemical developed a significantly higher proportion of tumors than did the control animals. As a part of these analyses, the one-tailed Fisher exact test (Cox, 1970, pp. 48-52) was used to compare the tumor incidence of a control group to that of a group of treated animals at each dose level. When results for a number of treated groups, k, are compared simultaneously with those for a control group, a correction to ensure an overall significance level of 0.05 may be made. The Bonferroni inequality (Miller, 1966, pp. 6-10) requires that the P-value for any comparison be less than or equal to 0.05/k. In cases where this correction was used, it is discussed in the narrative section. It is not, however, presented in the tables, where the Fisher exact P-values are shown.

The Cochran-Armitage test for linear trend in proportions, with continuity correction (Armitage, 1971, pp. 362-365), was also used when appropriate. Under the assumption of a linear trend, this test determined if the slope of the dose-response curve is different from zero at the one-tailed 0.05 level of significance. Unless otherwise noted, the direction of the significant trend was a positive dose relationship. This method also provides a two-tailed test of departure from linear trend.

A time-adjusted analysis was applied when numerous early deaths resulted from causes that were not associated with the formation of tumors. In this analysis, deaths that occurred before the first tumor was observed were excluded by basing the statistical tests on animals that survived at least 52 weeks, unless a tumor was found at the anatomic site of interest before week 52. When such an early tumor was found, comparisons were based exclusively on animals that survived at least as long as the animal in which the first tumor was found. Once this reduced set of data was obtained, the standard procedures for analyses of the incidence of tumors (Fisher exact tests, Cochran-Armitage tests, etc.) were followed.

When appropriate, life-table methods were used to analyze the incidence of tumors. Curves of the proportions surviving without an observed tumor were computed as in Saffiotti et al. (1972). The week during which animals died naturally or were sacrificed was entered as the time point of tumor observation. Cox's methods of comparing these curves were used for two groups; Tarone's extension to testing for linear trend was used for three groups. The statistical tests for the incidence of tumors which used life-table methods were one-tailed and, unless otherwise noted, in the direction of a positive dose relationship. Significant departures from linearity ($P < 0.05$, two-tailed test) were also noted.

The approximate 95 percent confidence interval for the relative risk of each dosed group compared to its control was calculated from the exact interval on the odds ratio (Gart, 1971). The relative risk is defined as p_t/p_c where p_t is the true binomial probability of the incidence of a specific type of tumor in a treated group of animals and p_c is the true probability of the spontaneous incidence of the same type of tumor in a control group. The hypothesis of equality between the true proportion of a specific tumor in a treated group and the proportion in a control group corresponds to a relative risk of unity. Values in excess of unity represent the condition of a larger proportion in the treated group than in the control.

The lower and upper limits of the confidence interval of the relative risk have been included in the tables of statistical analyses. The interpretation of the limits is that in approximately 95 percent of a large number of identical experiments, the true ratio of the risk in a treated group of animals to that in a control group would be within the interval calculated from the experiment. When the lower limit of the confidence interval is greater than one, it can be inferred that a statistically significant result (a $P < 0.025$ one-tailed test when the control incidence is not zero, $P < 0.050$ when the control incidence is zero) has occurred. When the lower limit is less than unity but the upper limit is greater than unity, the lower limit indicates the absence of a significant result while the upper limit indicates that there is a theoretical possibility of the induction of tumors by the test chemical which could not be detected under the conditions of this test.

III. CHRONIC TESTING RESULTS: RATS

A. Body Weights and Clinical Observations

Mean body weight of the high dose males was initially lower than that of the other male rats; however, this effect was only apparent until week 48. No appreciable differences in mean body weights were evident among female rats (Figure 1). Fluctuations in the growth curve may be due to mortality; as the size of the group diminishes, the mean body weight may be subject to wide variations.

Cutaneous/subcutaneous lesions were observed on the dorsal surface in one untreated control male, in the vaginal area in one low dose female, on the nose in one high dose male, on the tail in one high dose female, and behind the right foreleg in one vehicle control male. White discoloration of the eyes was apparent in two low dose females and one high dose male.

B. Survival

The estimated probabilities of survival for male and female rats in the control and m-cresidine-dosed groups are shown in Figure 2.

For male rats the Tarone test for positive association between dosage and mortality was significant when dosed groups were compared to the vehicle control. Five male rats were sacrificed from the untreated control group in week 79 and five from the high dose group in week 78. With 48 percent (24/50) of the high dose, 62 percent (31/50) of the low dose, 68 percent (17/25) of the vehicle control, and 64 percent (32/50) of the untreated control animals surviving on

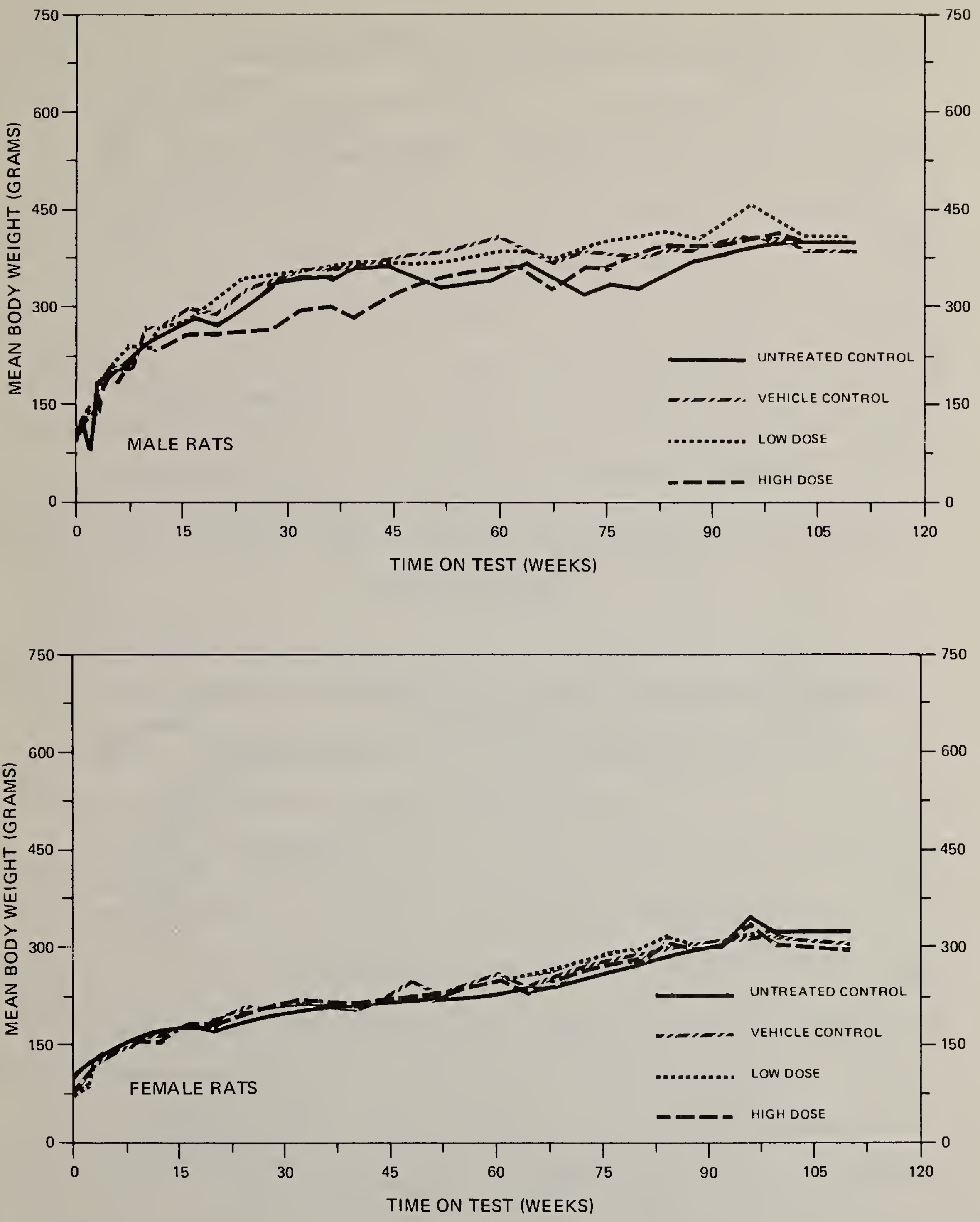

FIGURE 1
GROWTH CURVES FOR m-CRESIDINE CHRONIC STUDY RATS

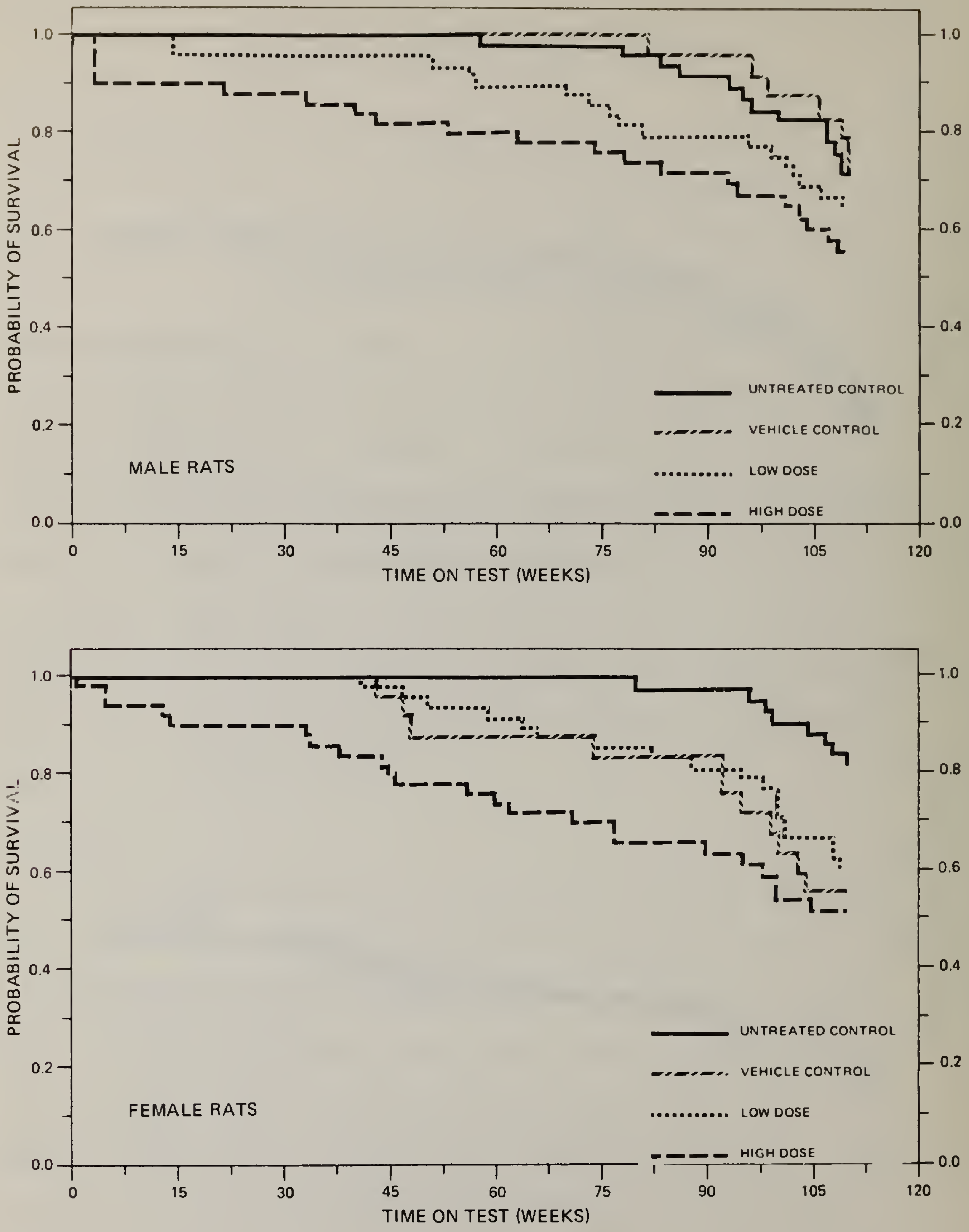

FIGURE 2
SURVIVAL COMPARISONS OF m-CRESIDINE CHRONIC STUDY RATS

test until the end of the study, adequate numbers of male rats were at risk from late-developing tumors.

For female rats the Cox test showed a significantly greater mortality in the high dose group than in the vehicle control group. Five females were sacrificed from the untreated control group in week 79 and five from the high dose group in week 78. With 44 percent (22/50) of the high dose, 57 percent (28/49) of the low dose, 52 percent (13/25) of the vehicle control, and 72 percent (36/50) of the untreated control animals alive on test until the end of the study, adequate numbers of female rats were at risk from late-developing tumors.

C. Pathology

Histopathologic findings on neoplasms in rats are summarized in Appendix A (Tables A1 and A2); findings on nonneoplastic lesions are summarized in Appendix C (Tables C1 and C2).

Compound- and dose-related neoplastic, hyperplastic, and degenerative lesions were limited to the urinary system. Papillary transitional-cell carcinomas of the urinary bladder occurred in 5/44 (11 percent) high dose males; 1/46 (2 percent) low dose females; and 2/44 (5 percent) high dose females. No animals in the low dose male, untreated control, or vehicle control groups developed bladder cancers. All of these tumors were papillary carcinomas which had a cauliflower-like pattern and grew into the lumen of the bladder. Microscopically, the transitional cells formed sheets which were supported by a fine fibrovascular stroma. The epithelial cells were slightly pleomorphic with oval, round, or irregularly shaped vesicular nuclei and frequently single prominent nucleoli. Occasional mitotic figures and invasion of the papillary stroma were noted. No invasion of the bladder wall or metastases were seen. Occasional polymorphonuclear leucocytes were present within cystic spaces in the tumor. In some tumors, there were numerous mast cells in the stroma. Occasional large vascular spaces containing blood or a pink proteinaceous material were noted in the stroma.

An additional compound- and dose-related lesion noted was epithelial hyperplasia of the renal pelvis. This change occurred in 26/45 (58 percent) high dose males and 29/45 (64 percent) high dose females. Normally, the renal papilla is covered by transitional epithelium 1 to 6 cells thick. Microscopically, the epithelial hyperplasia was characterized by irregularity of the surface of the renal pelvis and papilla and extensive epithelial proliferation, up to about 50 cells thick, with infolding of the papillary surface. Frequently, large hemocysts formed immediately beneath the epithelium. In addition, foci of mineralization and a fine fibrovascular stroma became incorporated into the epithelium.

Additional compound- and dose-related nephrotoxic lesions affected the renal papilla. Varying degrees and combinations of acute papillitis, hemorrhage, necrosis, and mineralization occurred which were distinctly different lesions from those associated with nephropathy in aged Fischer 344 rats. Varying degrees of architectural disarray of the renal papilla were observed. Collecting tubules were dilated and contained large amounts of granular and homogenous, pink, hyaline cast material. Occasionally, the casts showed basophilic stippling or a more uniform basophilia indicating mineralization. Polymorphonuclear leucocytes sometimes occurred in the lumen of collecting tubules. Scattered mononuclear cells and a few polymorphonuclear leucocytes occurred in the interstitium of the papilla. Slight to severe degrees of mineralization appeared to start at the basement membrane of collecting tubules and encroached upon necrotic tubular epithelial cells. Interstitial fibrosis was seen in these areas.

Spontaneous renal disease (recorded as nephrosis, nephropathy, or chronic glomerulonephritis) commonly observed in aged Fischer 344 rats occurred at a high but approximately equal incidence in all groups of both sexes; however, the severity of the lesions was much greater in animals treated with m-cresidine, suggesting that the compound enhanced a naturally occurring pathologic process in the Fischer 344 rat. Lesions were observed in the glomeruli, tubules, basement membranes, and the interstitium of the affected kidneys. The morphologic features observed were variable. The glomeruli varied from normal to shrunken, vacuolated, hyalinized, and sclerotic. Focal glomerular adhesions, thickening of capillary loops and increases in mesangial density were noted. Occasionally, Bowman's space was enlarged, and hyalinization of the basement membrane of Bowman's capsule occurred.

Varying degrees of tubular lesions were noted. Tubular degeneration and regeneration occurred. Focal tubules were dilated, lined by a flattened epithelium, and surrounded by a hyalinized basement membrane. Basement membrane hyalinization sometimes progressed to the point where the tubules were lost and only "ghost-like" basement membranes remained. In severely affected kidneys, focal areas of tubular destruction and loss were replaced by interstitial fibrosis. Varying degrees of tubular dilatation and accumulation of pink proteinaceous material within were noted. In severely affected animals treated with m-cresidine, "end-stage" renal disease occurred, with numerous dilated tubules filled with pink proteinaceous material. Occasional cysts were noted in the parenchyma.

A single tubular adenocarcinoma of the kidney occurred in the outer cortex of a high dose male. The center of the neoplasm was cystic and contained a light pink granular material. In some areas neoplastic epithelial cells formed tubular structures. There were moderate numbers of mitotic figures, and the mass was supported by a fine fibrovascular stroma.

The remaining neoplastic, proliferative, degenerative, and inflammatory lesions observed in control and treated rats were considered to be unrelated to compound administration and within the normal incidence limits in Fischer 344 rats.

This histopathologic examination provided evidence for carcinogenicity of m-cresidine to Fischer 344 rats. The compound induced transitional-cell carcinomas of the bladder. In addition, m-cresidine was nephrotoxic, inducing epithelial hyperplasia of the renal pelvis and renal papillae lesions; and an increased severity of spontaneous renal disease.

D. Statistical Analyses of Results

The results of the statistical analyses of tumor incidence in rats are summarized in Tables 3 and 4. The analysis is included for every type of primary tumor in either sex where at least two such tumors were observed in at least one of the control or m-cresidine-dosed groups and where such tumors were observed in at least 5 percent of the group.

For males the Cochran-Armitage test indicated a significant (P = 0.014) positive association between dose and the incidence of transitional-cell carcinomas of the urinary bladder. The Fisher exact tests, however, were not significant. In historical data collected by this laboratory for the NCI Carcinogenesis Testing Program none of the 250 male and 1/249 female untreated Fischer 344 rats had a tumor of the urinary bladder. Making the assumption of a binominal distribution with a probability of 1/251 of spontaneous incidence (the most conservative estimate), the probability of observing 5 or

TABLE 3

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT SPECIFIC SITES IN MALE RATS TREATED WITH m-CRESIDINE[a]

TOPOGRAPHY:MORPHOLOGY	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Skin and Subcutaneous Tissue: Fibroma[b]	3/25(0.12)	7/47(0.15)	4/45(0.09)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Vehicle Control)[d]	---	1.241	0.741
Lower Limit	---	0.318	0.138
Upper Limit	---	6.961	4.745
Weeks to First Observed Tumor	96	80	94
Skin and Subcutaneous Tissue: Fibrosarcoma[b]	0/25(0.00)	3/47(0.06)	0/45(0.00)
P Values[c]	N.S.	N.S.	N.S.
Departure from Linear Trend[e]	P = 0.035	---	---
Relative Risk (Vehicle Control)[d]	---	Infinite	---
Lower Limit	---	0.328	---
Upper Limit	---	Infinite	---
Weeks to First Observed Tumor	---	76	---
Lung: Alveolar/Bronchiolar Carcinoma[b]	0/25(0.00)	3/47(0.06)	2/44(0.05)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Vehicle Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.328	0.172
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	109	109

TABLE 3 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Hematopoietic System: Leukemia or Malignant Lymphoma[b]	0/25(0.00)	4/47(0.09)	1/45(0.02)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Vehicle Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.506	0.030
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	77	108
Liver: Hepatocellular Carcinoma or Neoplastic Nodule[b]	0/25(0.00)	4/47(0.09)	1/45(0.02)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Vehicle Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.506	0.030
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	99	109
Urinary Bladder: Transitional-Cell Carcinoma[b]	0/25(0.00)	0/45(0.00)	5/44(0.11)
P Values[c]	P = 0.014	N.S.	N.S.
Relative Risk (Vehicle Control)[d]	---	---	Infinite
Lower Limit	---	---	0.737
Upper Limit	---	---	Infinite
Weeks to First Observed Tumor	---	---	104

TABLE 3 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Pituitary: Adenoma NOS or Chromophobe Adenoma[b]	2/22(0.09)	6/45(0.13)	3/37(0.08)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Vehicle Control)[d]	---	1.467	0.892
Lower Limit	---	0.294	0.112
Upper Limit	---	14.114	10.101
Weeks to First Observed Tumor	110	70	78
Adrenal: Pheochromocytoma[b]	6/25(0.24)	6/47(0.13)	2/45(0.04)
P Values[c]	P = 0.013(N)	N.S.	P = 0.021(N)
Relative Risk (Vehicle Control)[d]	---	0.532	0.185
Lower Limit	---	0.162	0.020
Upper Limit	---	1.807	0.953
Weeks to First Observed Tumor	105	106	108
Thyroid: Follicular-Cell Carcinoma[b]	0/23(0.00)	1/44(0.02)	2/39(0.05)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Vehicle Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.029	0.180
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	95	109

TABLE 3 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Pancreatic Islets: Islet-Cell Adenoma or Islet-Cell Carcinoma[b]	1/24(0.04)	3/45(0.07)	2/41(0.05)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Vehicle Control)[d]	---	1.600	1.171
Lower Limit	---	0.139	0.065
Upper Limit	---	82.076	67.374
Weeks to First Observed Tumor	98	109	78
Body Cavities: Mesothelioma NOS or Mesothelioma, Malignant[b]	2/25(0.08)	0/47(0.00)	3/45(0.07)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Vehicle Control)[d]	---	0.000	0.833
Lower Limit	---	0.000	0.104
Upper Limit	---	1.789	9.528
Weeks to First Observed Tumor	110	---	104
Testis: Interstitial-Cell Tumor[b]	19/25(0.76)	35/45(0.78)	35/44(0.80)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Vehicle Control)[d]	---	1.023	1.047
Lower Limit	---	0.788	0.806
Upper Limit	---	1.414	1.432
Weeks to First Observed Tumor	98	95	74

TABLE 3 (CONCLUDED)

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[a] Treated groups received time-weighted average doses of 0.03 or 0.16 mg/kg body weight by gavage.

[b] Number of tumor-bearing animals/number of animals examined at site (proportion).

[c] The probability level for the Cochran-Armitage test is given beneath the incidence of tumors in the control group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. The probability level for the Fisher exact test for the comparison of a treated group with the control group is given beneath the incidence of tumors in the treated group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. For both Cochran-Armitage and Fisher exact tests a negative designation (N) indicates a lower incidence in the treated group(s) than in the control group.

[d] The 95% confidence interval on the relative risk of the treated group to the control group.

[e] The probability level of the test for departure from linear trend is given beneath the control group when $P < 0.05$.

TABLE 4

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT SPECIFIC SITES IN FEMALE RATS TREATED WITH m-CRESIDINE[a]

TOPOGRAPHY:MORPHOLOGY	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Lung: Alveolar/Bronchiolar Adenoma or Alveolar/Bronchiolar Carcinoma[b]	1/24(0.04)	3/49(0.06)	2/45(0.04)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Vehicle Control)[d]	---	1.469	1.067
Lower Limit	---	0.127	0.059
Upper Limit	---	75.534	61.532
Weeks to First Observed Tumor	104	109	110
Pituitary: Adenoma NOS or Chromophobe Adenoma[b]	7/23(0.30)	17/42(0.40)	8/36(0.22)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Vehicle Control)[d]	---	1.330	0.730
Lower Limit	---	0.634	0.274
Upper Limit	---	3.267	2.069
Weeks to First Observed Tumor	92	88	62
Thyroid: C-Cell Adenoma or C-Cell Carcinoma[b]	1/23(0.04)	4/45(0.09)	2/41(0.05)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Vehicle Control)[d]	---	2.044	1.122
Lower Limit	---	0.221	0.063
Upper Limit	---	98.348	64.580
Weeks to First Observed Tumor	110	109	110

TABLE 4 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Mammary Gland: Fibroadenoma[b]	3/24(0.13)	21/49(0.43)	8/46(0.17)
P Values[c]	N.S.	P = 0.008	N.S.
Departure from Linear Trend[e]	P = 0.001	---	---
Relative Risk (Vehicle Control)[d]	---	3.429	1.391
Lower Limit	---	1.182	0.377
Upper Limit	---	16.446	7.593
Weeks to First Observed Tumor	110	88	100
Mammary Gland: Adenoma NOS or Adenocarcinoma NOS[b]	2/24(0.08)	4/49(0.08)	1/46(0.02)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Vehicle Control)[d]	---	0.980	0.261
Lower Limit	---	0.154	0.005
Upper Limit	---	10.354	4.802
Weeks to First Observed Tumor	74	66	110
Uterus: Endometrial Stromal Polyp[b]	4/24(0.17)	8/47(0.17)	0/44(0.00)
P Values[c]	P = 0.012(N)	N.S.	P = 0.013(N)
Relative Risk (Vehicle Control)[d]	---	1.021	0.000
Lower Limit	---	0.312	0.000
Upper Limit	---	4.266	0.582
Weeks to First Observed Tumor	100	109	---

TABLE 4 (CONCLUDED)

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[a] Treated groups received time-weighted average doses of 0.08 or 0.16 mg/kg body weight by gavage.

[b] Number of tumor-bearing animals/number of animals examined at site (proportion).

[c] The probability level for the Cochran-Armitage test is given beneath the incidence of tumors in the control group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. The probability level for the Fisher exact test for the comparison of a treated group with the control group is given beneath the incidence of tumors in the treated group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. For both Cochran-Armitage and Fisher exact tests a negative designation (N) indicates a lower incidence in the treated group(s) than in the control group.

[d] The 95% confidence interval on the relative risk of the treated group to the control group.

[e] The probability level of the test for departure from linear trend is given beneath the control group when $P < 0.05$.

more animals with such tumors out of 44 males (as in the high dose group) was $P < 0.0001$, a significant result. Similar analyses for urinary bladder tumors did not give statistically significant numbers in the females.

For females the Fisher exact test indicated a significantly ($P = 0.008$) higher incidence of mammary fibroadenomas in the low dose group than in the control group. The high dose comparison and the Cochran-Armitage test, however, were not significant.

The possibility of a negative association between dose and incidence was noted for adrenal pheochromocytomas in males and for endometrial stromal polyps in females.

To provide additional insight into the possible carcinogenicity of this compound, 95 percent confidence intervals on the relative risk have been estimated and entered in the tables based upon the observed tumor incidence rates. In many of the intervals shown in Tables 3 and 4, the value one is included; this indicates the absence of statistically significant results. It should also be noted that many of the confidence intervals have an upper limit greater than one, indicating the theoretical possibility of tumor induction in rats by m-cresidine that could not be established under the conditions of this test.

IV. CHRONIC TESTING RESULTS: MICE

A. Body Weights and Clinical Observations

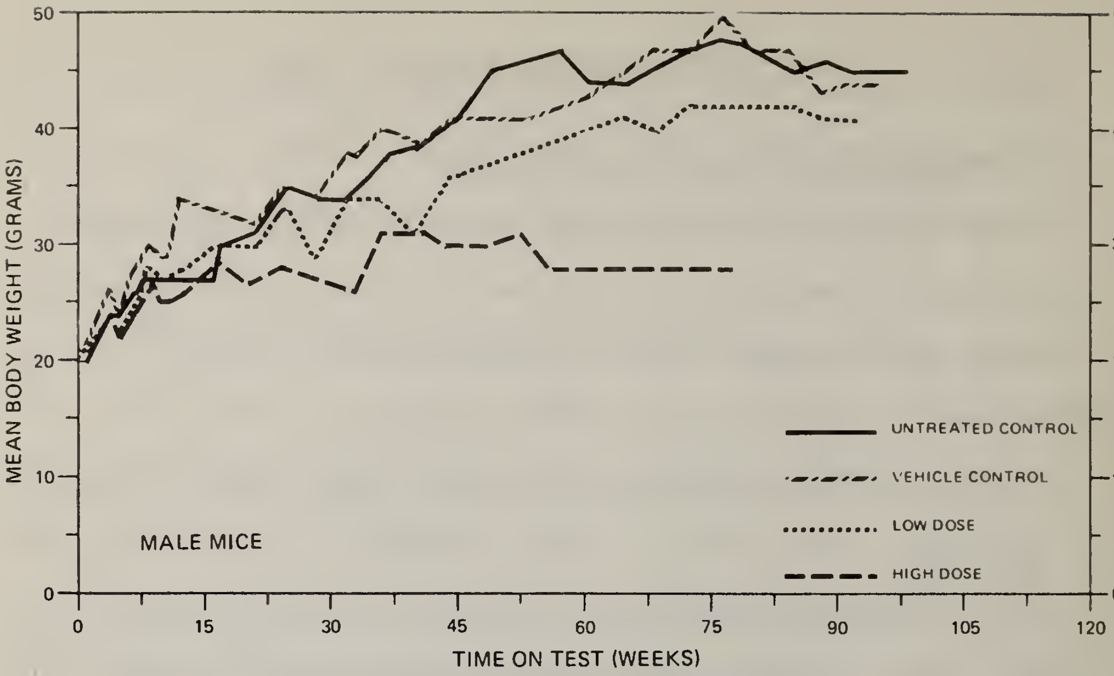
Growth curves for mice of both sexes were erratic (Figure 3). Fluctuations in the growth curve may be due to mortality; as the size of the group diminishes, the mean body weight may be subject to wide variations.

No clinical abnormalities were observed among mice of any group.

B. Survival

The estimated probabilities of survival for male and female mice in the control and m-cresidine-dosed groups are shown in Figure 4.

For male mice the Tarone test for positive association between dosage and mortality was significant ($P < 0.001$) when comparing the dosed groups to the vehicle control. The departure from linear trend was also significant ($P < 0.001$) due to accelerated mortality in the high dose group. Five animals were sacrificed from the untreated control group in week 80. Due to evidence of toxicity observed in weeks 26 through 28 in both treated groups, the dosages were lowered in week 33. Survival was very poor in the high dose treated group with a median survival of 26 weeks; the single surviving animal died at week 78. Survival was slightly better in the low dose treated group with a median survival of 52 weeks; 15 animals were still alive on test at the termination of the study. In both dosed groups sufficient numbers of male mice did not survive long enough to be at risk from late-developing tumors.



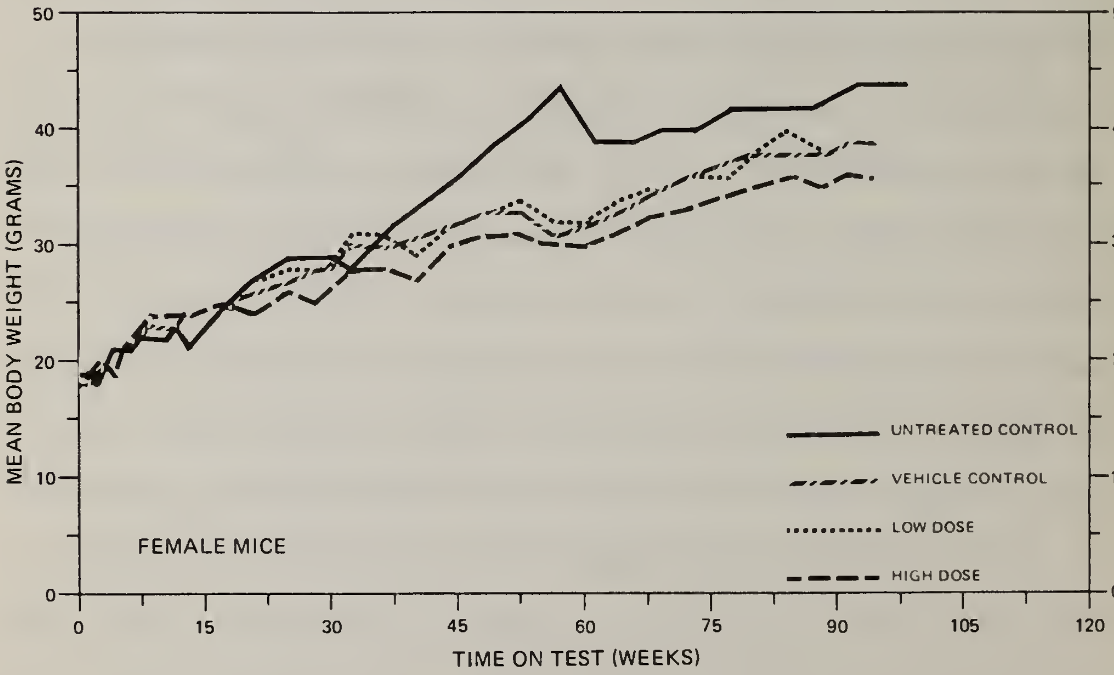


FIGURE 3
GROWTH CURVES FOR m-CRESIDINE CHRONIC STUDY MICE

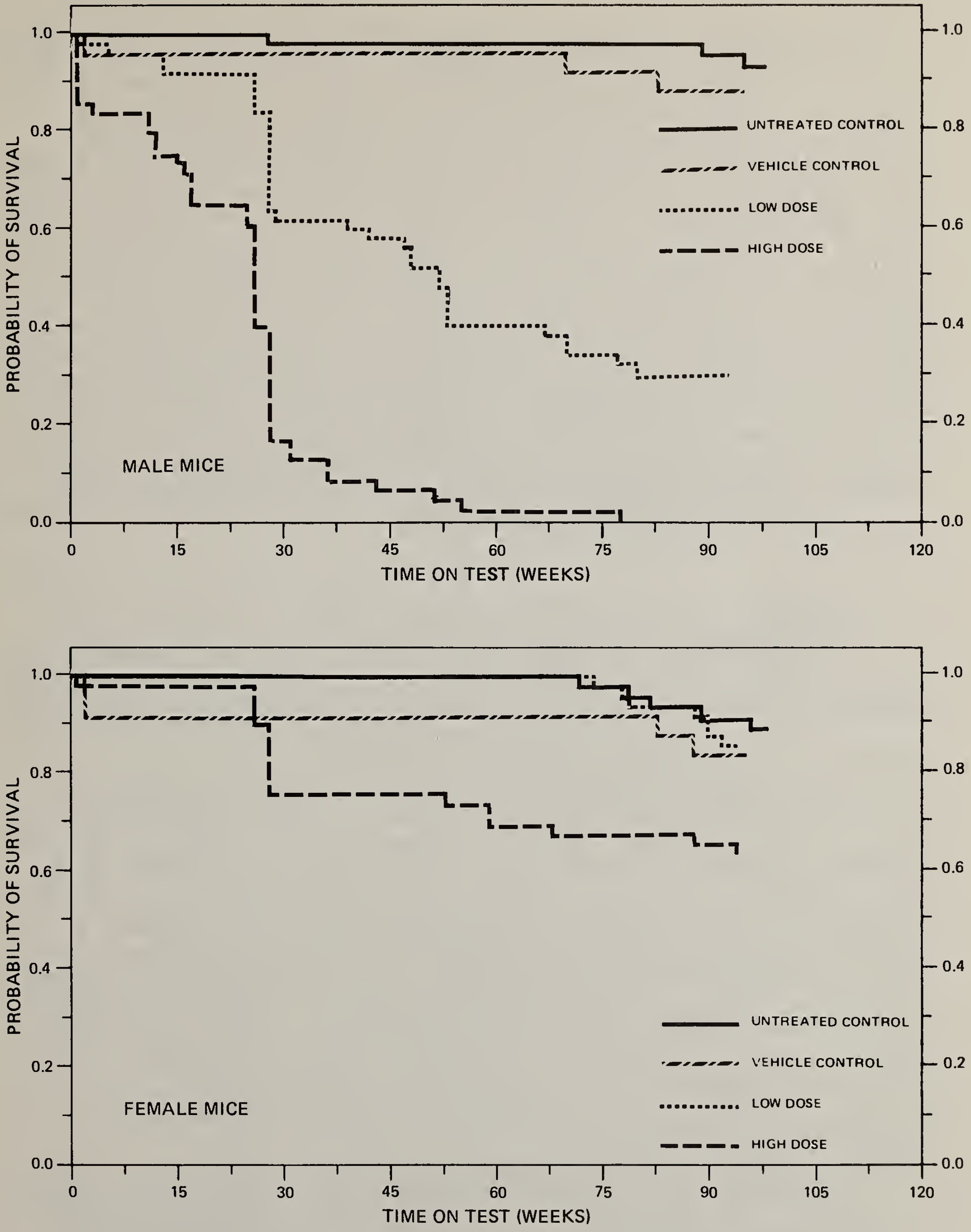


FIGURE 4
SURVIVAL COMPARISONS OF m-CRESIDINE CHRONIC STUDY MICE

For female mice the Cox test showed a significantly higher mortality in the high dose group than in the vehicle control group. Five animals were sacrificed from the untreated control group in week 80. Due to evidence of toxicity observed in weeks 26 through 28 in the high dose treated groups, the dosages were lowered in week 33. With 60 percent (30/50) of the high dose, 86 percent (43/50) low dose, 84 percent (21/25) vehicle control, and 80 percent (40/50) untreated control animals alive on test until the termination of the study, adequate numbers of female mice were at risk from late-developing tumors.

C. Pathology

Histopathologic findings on neoplasms in mice are summarized in Appendix B (Tables B1 and B2); findings on nonneoplastic lesions are summarized in Appendix D (Tables D1 and D2).

The incidence and type of neoplasms observed among control and treated mice were similar to those often occurring in B6C3F1 mice. Except for liver neoplasms in high dose females, there was no evidence of compound-related neoplasia. The lack of tumor development in high dose males and the lowered incidence of tumors in low dose males are attributed to early mortality caused by a nephrotoxic effect of the chemical.

Hepatocellular neoplasms (adenomas or carcinomas) were observed in 0/23 vehicle control, 1/50 (2 percent) low dose, and 5/45 (11 percent) high dose female mice. Since the number of liver neoplasms was not great and the natural incidence is variable, their distribution in female mice in this study might be due to chance.

Hepatocellular carcinoma was generally characterized by a mass composed of hepatocytes that produced compression of the adjacent parenchyma and lacked portal areas. Hepatocytes were basophilic, either small or large cell type, had vacuolated or granular cytoplasm, and had normal-sized or enlarged nuclei. Mitotic activity was minimal to moderate. Other changes included a trabecular growth pattern, one-cell thick or multiple-cell thick liver plates, and acinar formations which were often associated with moderate degrees of anaplasia. Occasional areas of necrosis were noted.

Hepatocellular carcinoma also occurred in male mice; however, there was no relationship to chemical administration, perhaps because of the shortened life spans of the treated male mice.

Nephrotoxic changes occurred in treated mice and were dose- and sex-related; being more pronounced in males. Principal renal lesions involved the tubules and renal papillae; glomeruli were usually spared. Tubular changes appeared as well-demarcated areas of degeneration and atrophy in the cortex. Degenerative cytoplasmic changes included vacuolation, reduction in volume and loss of acidophilia, with subsequent reduction in tubular diameters. Nuclei were often swollen and pale. Loss of tubular mass resulted in condensation of interstitial stroma and capsular depression overlying the affected areas. Necrosis of the renal papilla was frequently associated with the tubular lesions, especially in the treated male mice.

Additional dose-related lesions included atrophy of the thymus, spleen, and occasionally lymph nodes, and multinucleate (spermatidic) giant cells in the testes. Hepatocellular cytoplasmic vacuolation was common in chemically treated males.

This histopathologic examination did not provide evidence for the carcinogenecity of m-cresidine in B6C3F1 mice. However, m-cresidine was nephrotoxic in mice.

D. Statistical Analyses of Results

The results of the statistical analyses of tumor incidence in mice are summarized in Tables 5 and 6. The analysis is included for every type of primary tumor in either sex where at least two such tumors were observed in at least one of the control or m-cresidine-dosed groups and where such tumors were observed in at least 5 percent of the group. Due to the accelerated mortality in the treated males, the analyses of the males were based exclusively upon those mice surviving at least 52 weeks or, if the tumor of interest was observed earlier, surviving at least until the earliest tumor of interest was oberved.

For female mice when the incidences of hepatocellular adenomas and hepatocellular carcinomas were combined, the Cochran-Armitage test indicated a significant (P = 0.027) positive association between dose and incidence. The Fisher exact tests, however, were not

TABLE 5

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT SPECIFIC SITES IN MALE MICE TREATED WITH m-CRESIDINE SURVIVING AT LEAST 52 WEEKS[a,e]

TOPOGRAPHY:MORPHOLOGY	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Lung: Alveolar/Bronchiolar Carcinoma[b]	4/24(0.17)	1/23(0.04)	0/2(0.00)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Vehicle Control)[d]	---	0.261	0.000
Lower Limit	---	0.006	0.000
Upper Limit	---	2.380	6.649
Weeks to First Observed Tumor	70	93	---
Lung: Alveolar/Bronchiolar Adenoma or Alveolar/Bronchiolar Carcinoma[b,e]	4/24(0.17)	4/38(0.11)	0/17(0.00)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Vehicle Control)[d]	---	0.632	0.000
Lower Limit	---	0.131	0.000
Upper Limit	---	3.113	1.437
Weeks to First Observed Tumor	70	28	---
Hematopoietic System: Leukemia or Malignant Lymphoma[b]	2/24(0.08)	1/24(0.04)	0/2(0.00)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Vehicle Control)[d]	---	0.500	0.000
Lower Limit	---	0.001	0.000
Upper Limit	---	8.943	20.146
Weeks to First Observed Tumor	83	80	---

TABLE 5 (CONCLUDED)

TOPOGRAPHY:MORPHOLOGY	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Liver: Hepatocellular Carcinoma[b]	5/24(0.21)	3/22(0.14)	0/2(0.00)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Vehicle Control)[d]	---	0.655	0.000
Lower Limit	---	0.114	0.000
Upper Limit	---	2.941	4.925
Weeks to First Observed Tumor	95	93	---

---

[a] Treated groups received time-weighted average doses of 0.06 or 0.11 mg/kg body weight by gavage.

[b] Number of tumor-bearing animals/number of animals examined at site (proportion).

[c] The probability level for the Cochran-Armitage test is given beneath the incidence of tumors in the control group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. The probability level for the Fisher exact test for the comparison of a treated group with the control group is given beneath the incidence of tumors in the treated group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. For both Cochran-Armitage and Fisher exact tests a negative designation (N) indicates a lower incidence in the treated group(s) than in the control group.

[d] The 95% confidence interval on the relative risk of the treated group to the control group.

[e] For sites where the first tumor of interest was observed earlier than 52 weeks, the analyses were based upon all animals that survived until or past the date that the first tumor was observed.

TABLE 6

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT SPECIFIC SITES IN FEMALE MICE TREATED WITH m-CRESIDINE[a]

TOPOGRAPHY:MORPHOLOGY	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Lung: Alveolar/Bronchiolar Adenoma or Alveolar/Bronchiolar Carcinoma[b]	0/23(0.00)	2/49(0.04)	3/44(0.07)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Vehicle Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.143	0.324
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	93	94
Hematopoietic System: Malignant Lymphoma[b]	1/24(0.04)	4/50(0.08)	1/46(0.02)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Vehicle Control)[d]	---	1.920	0.522
Lower Limit	---	0.207	0.007
Upper Limit	---	92.583	40.096
Weeks to First Observed Tumor	94	79	94
Liver: Hepatocellular Carcinoma[b]	0/23(0.00)	1/50(0.02)	4/45(0.09)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Vehicle Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.025	0.489
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	94	94

TABLE 6 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Liver: Hepatocellular Adenoma or Hepatocellular Carcinoma[b]	0/23(0.00)	1/50(0.02)	5/45(0.11)
P Values[c]	P = 0.027	N.S.	N.S.
Relative Risk (Vehicle Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.025	0.666
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	94	94
Pituitary: Adenoma NOS[b]	0/17(0.00)	2/34(0.06)	0/31(0.00)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Vehicle Control)[d]	---	Infinite	---
Lower Limit	---	0.155	---
Upper Limit	---	Infinite	---
Weeks to First Observed Tumor	---	93	---
Ovary: Cystadenoma NOS[b]	0/20(0.00)	0/39(0.00)	2/41(0.05)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Vehicle Control)[d]	---	---	Infinite
Lower Limit	---	---	0.150
Upper Limit	---	---	Infinite
Weeks to First Observed Tumor	---	---	53

TABLE 6 (CONCLUDED)

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[a] Treated groups received time-weighted average doses of 0.06 or 0.11 mg/kg body weight by gavage.

[b] Number of tumor-bearing animals/number of animals examined at site (proportion).

[c] The probability level for the Cochran-Armitage test is given beneath the incidence of tumors in the control group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. The probability level for the Fisher exact test for the comparison of a treated group with the control group is given beneath the incidence of tumors in the treated group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. For both Cochran-Armitage and Fisher exact tests a negative designation (N) indicates a lower incidence in the treated group(s) than in the control group.

[d] The 95% confidence interval on the relative risk of the treated group to the control group.

[e] The probability level of the test for departure from linear trend is given beneath the control group when $P < 0.05$.

significant. No other statistically significant results were observed for either male or female mice.

Based upon these results there was no statistical evidence that m-cresidine was a carcinogen in mice.

To provide additional insight into the possible carcinogenicity of this compound, 95 percent confidence intervals on the relative risk have been estimated and entered in the tables based upon the observed tumor incidence rates. In all of the intervals shown in Tables 5 and 6, the value one is included; this indicates the absence of statistically significant results. It should also be noted that all of the confidence intervals have an upper limit greater than one, indicating the theoretical possibility of tumor induction in mice by m-cresidine that could not be established under the conditions of this test.

V. DISCUSSION

A high rate of dose-related mortality was observed among male mice. In all other groups in this bioassay, adequate numbers of animals survived long enough to be at risk from late-developing tumors.

Among rats dose-related lesions were limited to the urinary system. Papillary transitional-cell carcinomas of the urinary bladder occurred in 5/44 (11 percent) high dose males, 1/46 (2 percent) low dose females, and 2/44 (5 percent) high dose females. No bladder tumors were observed among rats in the low dose male group, untreated control groups or vehicle control groups. The Cochran-Armitage test indicated a significant positive relationship between dose and the incidence of papillary transitional-cell carcinomas of the urinary bladder for male rats but not for females. According to the Fisher exact test results, no group of dosed rats had this tumor at an incidence significantly higher than the corresponding vehicle control group. When a binomial distribution and a spontaneous incidence for this neoplasm of 1/251 were assumed, the observation of 5 or more animals with such neoplasms out of a group of 44, as in the high dose male rats, was a significant event. The incidence observed in female rats did not provide a similar, statistically significant result; however, these tumors occur rarely in control female rats (1/249 in the historical controls) and the incidence observed in dosed female rats in this bioassay is considered to be biologically important evidence for the carcinogenicity of m-cresidine in these rats.

A single tubular-cell adenocarcinoma of the kidney occurred in one high dose male rat. Epithelial hyperplasia of the renal pelvis was observed in 26/45 (58 percent) high dose male rats and 29/45 (64 percent) of the high dose female rats, but not in low dose or control rat groups. Mineralization of the renal papilla was observed in 7/47 (15 percent) low dose males, 27/45 (60 percent) high dose males, 3/49 (6 percent) low dose females, and in 34/45 (76 percent) high dose females, but in no untreated or vehicle control rats. Renal lesions (nephrosis, nephropathy or glomerulonephritis) commonly occurring in aged Fischer 344 rats occurred at a similar incidence in dosed and control rats, but the severity of the lesions was much greater in animals dosed with m-cresidine, suggesting that the compound enhanced a naturally occurring pathologic process.

Among female mice, there was a significant positive association between the incidence of hepatocellular neoplasms (adenomas and/or carcinomas) and dosage; however the incidence was not significantly greater in either the low dose or the high dose group than in the vehicle control group.

Dose-related toxic effects observed at higher incidences in male mice than female mice include nephrotoxicity (necrosis of renal papilla and nephrosis) and atrophy of the spleen and thymus. The presence of multinucleate (spermatidic) giant cells in the testes were also dose-related in male mice. Since the same dosages were administered to both sexes, the high incidences of these toxic effects and associated accelerated mortality among male mice indicates that male mice were more sensitive than females to m-cresidine toxicity.

Under the conditions of this bioassay, m-cresidine was carcinogenic to Fischer 344 rats, causing papillary transitional-cell carcinomas of the urinary bladder in both sexes. No convincing evidence was provided for carcinogenicity in female B6C3F1 mice. Poor survival of male B6C3F1 mice receiving m-cresidine precluded evaluation of the possible carcinogenicity of this compound in these animals.

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS TREATED WITH m-CRESIDINE

TABLE A1
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS TREATED WITH m-CRESIDINE

	CONTROL (UNTR) 01-0160	CONTROL (VEH) 01-0175	LOW DOSE 01-0165	HIGH DOSE 01-0170
ANIMALS INITIALLY IN STUDY	50	25	50	50
ANIMALS NECROPSIED	50	25	47	45
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	50	25	47	45
INTEGUMENTARY SYSTEM				
*SKIN	(50)	(25)	(47)	(45)
SQUAMOUS CELL PAPILLOMA			1 (2%)	
SQUAMOUS CELL CARCINOMA		1 (4%)	1 (2%)	1 (2%)
BASAL-CELL CARCINOMA			1 (2%)	
FIBROMA	1 (2%)		2 (4%)	4 (9%)
FIBROSARCOMA	1 (2%)			
*SUBCUT TISSUE	(50)	(25)	(47)	(45)
SARCOMA, NOS	1 (2%)			
FIBROMA	1 (2%)	3 (12%)	5 (11%)	
FIBROSARCOMA	1 (2%)		3 (6%)	
LIPOMA		1 (4%)		
RESPIRATORY SYSTEM				
#LUNG	(49)	(25)	(47)	(44)
HEPATOCELLULAR CARCINOMA, METAST			1 (2%)	
ALVEOLAR/BRONCHIOLAR ADENOMA				1 (2%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (2%)		3 (6%)	2 (5%)
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(50)	(25)	(47)	(45)
MALIGNANT LYMPHOMA, NOS			1 (2%)	
LEUKEMIA, NOS	1 (2%)			
MYELOMONOCYTIC LEUKEMIA	9 (18%)		1 (2%)	1 (2%)
#SPLEEN	(50)	(25)	(47)	(43)
MYELOMONOCYTIC LEUKEMIA			2 (4%)	
CIRCULATORY SYSTEM				
#HEART	(48)	(25)	(47)	(44)
SARCOMA, NOS, METASTATIC	1 (2%)			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE A1 (CONTINUED)

	CONTROL (UNTR) 01-0160	CONTROL (VEH) 01-0175	LOW DOSE 01-0165	HIGH DOSE 01-0170
DIGESTIVE SYSTEM				
#LIVER	(49)	(25)	(47)	(45)
NEOPLASTIC NODULE			2 (4%)	
HEPATOCELLULAR CARCINOMA			2 (4%)	1 (2%)
#SMALL INTESTINE	(49)	(25)	(45)	(43)
LEIOMYOSARCOMA		1 (4%)		
#JEJUNUM	(49)	(25)	(45)	(43)
ADENOCARCINOMA, NOS				1 (2%)
#ILEUM	(49)	(25)	(45)	(43)
LEIOMYOSARCOMA		1 (4%)		
URINARY SYSTEM				
#KIDNEY	(50)	(25)	(47)	(45)
TUBULAR-CELL ADENOCARCINOMA				1 (2%)
#URINARY BLADDER	(50)	(25)	(45)	(44)
TRANSITIONAL-CELL CARCINOMA				5 (11%)
ENDOCRINE SYSTEM				
#PITUITARY	(45)	(22)	(45)	(37)
ADENOMA, NOS	5 (11%)		2 (4%)	3 (8%)
CHROMOPHOBE ADENOMA	2 (4%)	2 (9%)	4 (9%)	
#ADRENAL	(50)	(25)	(47)	(45)
PHEOCHROMOCYTOMA	3 (6%)	6 (24%)	6 (13%)	2 (4%)
#THYROID	(37)	(23)	(44)	(39)
FOLLICULAR-CELL CARCINOMA	1 (3%)		1 (2%)	2 (5%)
C-CELL ADENOMA	1 (3%)	1 (4%)	1 (2%)	
C-CELL CARCINOMA	2 (5%)		1 (2%)	1 (3%)
#PANCREATIC ISLETS	(47)	(24)	(45)	(41)
ISLET-CELL ADENOMA	1 (2%)	1 (4%)	2 (4%)	2 (5%)
ISLET-CELL CARCINOMA			1 (2%)	
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(50)	(25)	(47)	(45)
FIBROADENOMA			1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A1 (CONTINUED)

	CONTROL (UNTR) 01-0160	CONTROL (VEH) 01-0175	LOW DOSE 01-0165	HIGH DOSE 01-0170
*PREPUTIAL GLAND	(50)	(25)	(47)	(45)
CARCINOMA,NOS	2 (4%)			
SEBACEOUS ADENOMA			1 (2%)	
#TESTIS	(50)	(25)	(45)	(44)
INTERSTITIAL-CELL TUMOR	42 (84%)	19 (76%)	35 (78%)	35 (80%)
NERVOUS SYSTEM				
#BRAIN	(50)	(24)	(45)	(42)
GLIOMA, NOS			1 (2%)	
#CEREBRAL CORTEX	(50)	(24)	(45)	(42)
GLIOMA, NOS	1 (2%)			
SPECIAL SENSE ORGANS				
*EAR	(50)	(25)	(47)	(45)
SQUAMOUS CELL CARCINOMA			1 (2%)	
MUSCULOSKELETAL SYSTEM				
*BONE	(50)	(25)	(47)	(45)
FIBROSARCOMA, INVASIVE			1 (2%)	
BODY CAVITIES				
*BODY CAVITIES	(50)	(25)	(47)	(45)
MESOTHELIOMA, NOS		1 (4%)		2 (4%)
MESOTHELIOMA, MALIGNANT		1 (4%)		1 (2%)
*PERITONEUM	(50)	(25)	(47)	(45)
SQUAMOUS CELL CARCINOMA, INVASIV			1 (2%)	
ALL OTHER SYSTEMS				
NONE				

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A1 (CONCLUDED)

	CONTROL (UNTR) 01-0160	CONTROL (VEH) 01-0175	LOW DOSE 01-0165	HIGH DOSE 01-0170
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	50	25	50	50
NATURAL DEATH@	5	6	10	14
MORIBUND SACRIFICE	8	1	7	7
SCHEDULED SACRIFICE	5			5
ACCIDENTALLY KILLED		1	2	
TERMINAL SACRIFICE	32	17	31	24
ANIMAL MISSING				

@ INCLUDES AUTOLYZED ANIMALS

	CONTROL (UNTR) 01-0160	CONTROL (VEH) 01-0175	LOW DOSE 01-0165	HIGH DOSE 01-0170
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	49	24	41	36
TOTAL PRIMARY TUMORS	76	38	81	65
TOTAL ANIMALS WITH BENIGN TUMORS	46	23	39	36
TOTAL BENIGN TUMORS	56	33	60	47
TOTAL ANIMALS WITH MALIGNANT TUMORS	17	3	15	14
TOTAL MALIGNANT TUMORS	20	4	19	16
TOTAL ANIMALS WITH SECONDARY TUMORS#	1		3	
TOTAL SECONDARY TUMORS	1		3	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT		1	2	2
TOTAL UNCERTAIN TUMORS		1	2	2
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

TABLE A2

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS TREATED WITH m-CRESIDINE

	CONTROL (UNTR) 02-0160	CONTROL (VEH) 02-0175	LOW DOSE 02-0165	HIGH DOSE 02-0170
ANIMALS INITIALLY IN STUDY	50	25	@49	50
ANIMALS MISSING	1			
ANIMALS NECROPSIED	49	24	49	46
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	49	24	49	45
INTEGUMENTARY SYSTEM				
*SKIN	(49)	(24)	(49)	(46)
SQUAMOUS CELL PAPILLOMA			1 (2%)	
SQUAMOUS CELL CARCINOMA			1 (2%)	
FIBROMA				1 (2%)
*SUBCUT TISSUE	(49)	(24)	(49)	(46)
FIBROMA	2 (4%)			
LIPOMA			1 (2%)	
RESPIRATORY SYSTEM				
#LUNG	(49)	(24)	(49)	(45)
ADENOCARCINOMA, NOS, METASTATIC			1 (2%)	
ALVEOLAR/BRONCHIOLAR ADENOMA			3 (6%)	
ALVEOLAR/BRONCHIOLAR CARCINOMA		1 (4%)		2 (4%)
OSTEOSARCOMA, METASTATIC			1 (2%)	
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(49)	(24)	(49)	(46)
LEUKEMIA, NOS	1 (2%)			
MYELOMONOCYTIC LEUKEMIA	6 (12%)			
#BONE MARROW	(45)	(24)	(47)	(44)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)	
CIRCULATORY SYSTEM				
#HEART	(48)	(24)	(48)	(45)
FIBROSARCOMA			1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY

* NUMBER OF ANIMALS NECROPSIED

**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

@NOTE: 50 ANIMALS WERE INITIALLY IN STUDY BUT ONE WAS FOUND TO BE A MALE IN A FEMALE GROUP AND WAS DELETED.

TABLE A2 (CONTINUED)

	CONTROL (UNTR) 02-0160	CONTROL (VEH) 02-0175	LOW DOSE 02-0165	HIGH DOSE 02-0170
DIGESTIVE SYSTEM				
#LIVER	(48)	(24)	(49)	(44)
HEPATOCELLULAR CARCINOMA	1 (2%)		1 (2%)	1 (2%)
URINARY SYSTEM				
#URINARY BLADDER	(49)	(24)	(46)	(44)
TRANSITIONAL-CELL CARCINOMA			1 (2%)	2 (5%)
ENDOCRINE SYSTEM				
#PITUITARY	(39)	(23)	(42)	(36)
ADENOMA, NOS	15 (38%)		15 (36%)	8 (22%)
CHROMOPHOBE ADENOMA	2 (5%)	7 (30%)	2 (5%)	
#ADRENAL	(49)	(24)	(47)	(45)
CORTICAL ADENOMA			2 (4%)	
PHEOCHROMOCYTOMA	3 (6%)			1 (2%)
#THYROID	(45)	(23)	(45)	(41)
FOLLICULAR-CELL ADENOMA				1 (2%)
FOLLICULAR-CELL CARCINOMA			1 (2%)	1 (2%)
C-CELL ADENOMA			3 (7%)	2 (5%)
C-CELL CARCINOMA	2 (4%)	1 (4%)	1 (2%)	
#PANCREATIC ISLETS	(48)	(23)	(46)	(42)
ISLET-CELL CARCINOMA				1 (2%)
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(49)	(24)	(49)	(46)
ADENOMA, NOS		1 (4%)	3 (6%)	1 (2%)
ADENOCARCINOMA, NOS		1 (4%)	1 (2%)	
PAPILLARY ADENOCARCINOMA			1 (2%)	
FIBROMA		1 (4%)		
FIBROADENOMA	12 (24%)	3 (13%)	21 (43%)	8 (17%)
*CLITORAL GLAND	(49)	(24)	(49)	(46)
CARCINOMA, NOS			1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A2 (CONTINUED)

	CONTROL (UNTR) 02-0160	CONTROL (VEH) 02-0175	LOW DOSE 02-0165	HIGH DOSE 02-0170
ADENOMA, NOS	1 (2%)		1 (2%)	
#UTERUS	(46)	(24)	(47)	(44)
CARCINOMA, NOS, INVASIVE				1 (2%)
ENDOMETRIAL STROMAL POLYP	5 (11%)	4 (17%)	8 (17%)	
#CERVIX UTERI	(46)	(24)	(47)	(44)
FIBROMA			1 (2%)	
#UTERUS/ENDOMETRIUM	(46)	(24)	(47)	(44)
ADENOCARCINOMA, NOS			1 (2%)	
NERVOUS SYSTEM				
#BRAIN	(49)	(24)	(47)	(43)
GLIOMA, NOS			1 (2%)	
ASTROCYTOMA	1 (2%)			
OLIGODENDROGLIOMA			1 (2%)	
SPECIAL SENSE ORGANS				
*ZYMBAL'S GLAND	(49)	(24)	(49)	(46)
CERUMINOUS CARCINOMA	1 (2%)			
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
LOWER LEG				
OSTEOSARCOMA				

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A2 (CONCLUDED)

	CONTROL (UNTR) 02-0160	CONTROL (VEH) 02-0175	LOW DOSE 02-0165	HIGH DOSE 02-0170
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	50	25	50	50
NATURAL DEATH@	2	9	11	17
MORIBUND SACRIFICE	6	3	9	6
SCHEDULED SACRIFICE	5			5
ACCIDENTALLY KILLED			1	
TERMINAL SACRIFICE	36	13	28	22
ANIMAL MISSING	1			
ANIMAL DELETED (WRONG SEX)			1	

@ INCLUDES AUTOLYZED ANIMALS

	CONTROL (UNTR) 02-0160	CONTROL (VEH) 02-0175	LOW DOSE 02-0165	HIGH DOSE 02-0170
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	31	12	38	19
TOTAL PRIMARY TUMORS	52	19	75	29
TOTAL ANIMALS WITH BENIGN TUMORS	27	10	34	16
TOTAL BENIGN TUMORS	40	16	61	22
TOTAL ANIMALS WITH MALIGNANT TUMORS	10	3	14	6
TOTAL MALIGNANT TUMORS	12	3	14	7
TOTAL ANIMALS WITH SECONDARY TUMORS#			2	1
TOTAL SECONDARY TUMORS			2	1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT				
TOTAL UNCERTAIN TUMORS				
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS

# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE TREATED WITH m-CRESIDINE

TABLE B1
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE TREATED WITH m-CRESIDINE

	CONTROL (UNTR) 05-0160	CONTROL (VEH) 05-0175	LOW DOSE 05-0165	HIGH DOSE 05-0170
ANIMALS INITIALLY IN STUDY	50	25	50	50
ANIMALS MISSING				1
ANIMALS NECROPSIED	50	24	46	41
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	49	24	45	36
INTEGUMENTARY SYSTEM				
NONE				
RESPIRATORY SYSTEM				
#LUNG	(47)	(24)	(44)	(36)
HEPATOCELLULAR CARCINOMA, METAST	2 (4%)			
ALVEOLAR/BRONCHIOLAR ADENOMA	4 (9%)		3 (7%)	
ALVEOLAR/BRONCHIOLAR CARCINOMA	3 (6%)	4 (17%)	1 (2%)	
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(50)	(24)	(46)	(41)
MALIGNANT LYMPHOMA, NOS	1 (2%)			
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		1 (4%)	1 (2%)	
GRANULOCYTIC LEUKEMIA		1 (4%)		
#SPLEEN	(49)	(24)	(41)	(32)
HEMANGIOSARCOMA	1 (2%)		1 (2%)	
HAMARTOMA			1 (2%)	
#MESENTERIC L. NODE	(40)	(20)	(31)	(26)
SARCOMA, NOS			1 (3%)	
CIRCULATORY SYSTEM				
NONE				
DIGESTIVE SYSTEM				
#LIVER	(49)	(24)	(44)	(36)
HEPATOCELLULAR CARCINOMA	15 (31%)	5 (21%)	3 (7%)	

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE B1 (CONTINUED)

	CONTROL (UNTR) 05-0160	CONTROL (VEH) 05-0175	LOW DOSE 05-0165	HIGH DOSE 05-0170
#STOMACH	(49)	(24)	(39)	(35)
ADENOMATOUS POLYP, NOS	1 (2%)			
URINARY SYSTEM				
NONE				
ENDOCRINE SYSTEM				
#THYROID	(42)	(22)	(34)	(28)
FOLLICULAR-CELL CARCINOMA			1 (3%)	
REPRODUCTIVE SYSTEM				
#TESTIS	(49)	(24)	(41)	(35)
INTERSTITIAL-CELL TUMOR	1 (2%)			
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
NONE				

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B 1(CONCLUDED)

	CONTROL(UNTR) 05-0160	CONTROL(VEH) 05-0175	LOW DOSE 05-0165	HIGH DOSE 05-0170
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	50	25	50	50
NATURAL DEATH@	3	3	27	32
MORIBUND SACRIFICE			8	16
SCHEDULED SACRIFICE	5			
ACCIDENTALLY KILLED				1
TERMINAL SACRIFICE	42	22	15	
ANIMAL MISSING				1

@ INCLUDES AUTOLYZED ANIMALS

	CONTROL(UNTR) 05-0160	CONTROL(VEH) 05-0175	LOW DOSE 05-0165	HIGH DOSE 05-0170
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	20	9	10	
TOTAL PRIMARY TUMORS	26	11	12	
TOTAL ANIMALS WITH BENIGN TUMORS	6		4	
TOTAL BENIGN TUMORS	6		4	
TOTAL ANIMALS WITH MALIGNANT TUMORS	18	9	7	
TOTAL MALIGNANT TUMORS	20	11	8	
TOTAL ANIMALS WITH SECONDARY TUMORS#	2			
TOTAL SECONDARY TUMORS	2			
TOTAL ANIMALS WITH TUMORS UNCERTAIN- BENIGN OR MALIGNANT				
TOTAL UNCERTAIN TUMORS				
TOTAL ANIMALS WITH TUMORS UNCERTAIN- PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

TABLE B2
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE TREATED WITH m-CRESIDINE

	CONTROL (UNTR) 06-0160	CONTROL (VEH) 06-0175	LOW DOSE 06-0165	HIGH DOSE 06-0170
ANIMALS INITIALLY IN STUDY	50	25	50	50
ANIMALS MISSING				2
ANIMALS NECROPSIED	50	24	50	46
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	50	24	50	46
INTEGUMENTARY SYSTEM				
*SKIN	(50)	(24)	(50)	(46)
HEMANGIOMA				1 (2%)
*SUBCUT TISSUE	(50)	(24)	(50)	(46)
FIBROSARCOMA	1 (2%)	1 (4%)		
HEMANGIOSARCOMA	1 (2%)			
NEURILEMOMA, MALIGNANT			1 (2%)	
RESPIRATORY SYSTEM				
#LUNG	(50)	(23)	(49)	(44)
HEPATOCELLULAR CARCINOMA, METAST	1 (2%)			
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (2%)		1 (2%)	1 (2%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	3 (6%)		1 (2%)	2 (5%)
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(50)	(24)	(50)	(46)
MALIGNANT LYMPHOMA, NOS	3 (6%)		1 (2%)	
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE			3 (6%)	1 (2%)
#SPLEEN	(49)	(23)	(49)	(43)
HEMANGIOMA			1 (2%)	
HEMANGIOSARCOMA	1 (2%)			
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)			
#MANDIBULAR L. NODE	(40)	(18)	(41)	(40)
MALIGNANT LYMPHOMA, NOS	1 (3%)			
#MESENTERIC L. NODE	(40)	(18)	(41)	(40)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		1 (6%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE B2 (CONTINUED)

	CONTROL(UNTR) 06-0160	CONTROL(VEH) 06-0175	LOW DOSE 06-0165	HIGH DOSE 06-0170
#PEYERS PATCH	(49)	(24)	(47)	(42)
MALIGNANT LYMPHOMA, NOS	1 (2%)			
CIRCULATORY SYSTEM				
NONE				
DIGESTIVE SYSTEM				
#LIVER	(49)	(23)	(50)	(45)
HEPATOCELLULAR ADENOMA				1 (2%)
HEPATOCELLULAR CARCINOMA	2 (4%)		1 (2%)	4 (9%)
ANGIOSARCOMA				1 (2%)
URINARY SYSTEM				
NONE				
ENDOCRINE SYSTEM				
#PITUITARY	(42)	(17)	(34)	(31)
ADENOMA, NOS			2 (6%)	
#THYROID	(41)	(17)	(36)	(32)
FOLLICULAR-CELL ADENOMA				1 (3%)
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(50)	(24)	(50)	(46)
PAPILLARY ADENOCARCINOMA				1 (2%)
#UTERUS	(49)	(22)	(46)	(42)
HEMANGIOMA		1 (5%)		
#OVARY	(48)	(20)	(39)	(41)
CYSTADENOMA, NOS				2 (5%)
NERVOUS SYSTEM				
NONE				

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B2 (CONTINUED)

	CONTROL (UNTR) 06-0160	CONTROL (VEH) 06-0175	LOW DOSE 06-0165	HIGH DOSE 06-0170
SPECIAL SENSE ORGANS				
*EYE/LACRIMAL GLAND	(50)	(24)	(50)	(46)
PAPILLARY ADENOMA				1 (2%)
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
NONE				
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	50	25	50	50
NATURAL DEATH@	3	4	6	9
MORIBUND SACRIFICE	2		1	9
SCHEDULED SACRIFICE	5			
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	40	21	43	30
ANIMAL MISSING				2

@ INCLUDES AUTOLYZED ANIMALS

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B2 (CONCLUDED)

	CONTROL (UNTR) 06-0160	CONTROL (VEH) 06-0175	LOW DOSE 06-0165	HIGH DOSE 06-0170
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	12	3	10	15
TOTAL PRIMARY TUMORS	15	3	11	16
TOTAL ANIMALS WITH BENIGN TUMORS	1	1	4	7
TOTAL BENIGN TUMORS	1	1	4	7
TOTAL ANIMALS WITH MALIGNANT TUMORS	11	2	7	9
TOTAL MALIGNANT TUMORS	14	2	7	9
TOTAL ANIMALS WITH SECONDARY TUMORS#	1			
TOTAL SECONDARY TUMORS	1			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT				
TOTAL UNCERTAIN TUMORS				
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS TREATED WITH m-CRESIDINE

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TABLE C1
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS TREATED WITH m-CRESIDINE

	CONTROL (UNTR) 01-0160	CONTROL (VEH) 01-0175	LOW DOSE 01-0165	HIGH DOSE 01-0170
ANIMALS INITIALLY IN STUDY	50	25	50	50
ANIMALS NECROPSIED	50	25	47	45
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	50	25	47	45
INTEGUMENTARY SYSTEM				
*SKIN	(50)	(25)	(47)	(45)
INFLAMMATION, NOS			1 (2%)	
ULCER, FOCAL			1 (2%)	
INFLAMMATION, SUPPURATIVE	1 (2%)			
HYPERPLASIA, BASAL CELL			1 (2%)	1 (2%)
RESPIRATORY SYSTEM				
*LARYNX	(50)	(25)	(47)	(45)
NECROSIS, NOS				1 (2%)
#LUNG	(49)	(25)	(47)	(44)
CONGESTION, NOS		4 (16%)	1 (2%)	4 (9%)
CONGESTION, CHRONIC PASSIVE	1 (2%)			
EDEMA, NOS		2 (8%)	1 (2%)	
HEMORRHAGE			2 (4%)	
INFLAMMATION, FOCAL				2 (5%)
INFLAMMATION, INTERSTITIAL	4 (8%)		1 (2%)	
BRONCHOPNEUMONIA, ACUTE			1 (2%)	
INFLAMMATION, FOCAL GRANULOMATOU			1 (2%)	
FIBROSIS, DIFFUSE	1 (2%)			
PERIVASCULITIS			1 (2%)	
HYPERPLASIA, NOS	1 (2%)			
HYPERPLASIA, ALVEOLAR EPITHELIUM	1 (2%)		6 (13%)	
#LUNG/ALVEOLI	(49)	(25)	(47)	(44)
HEMORRHAGE	1 (2%)			
HEMATOPOIETIC SYSTEM				
#SPLEEN	(50)	(25)	(47)	(43)
FIBROSIS	1 (2%)			

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE C1 (CONTINUED)

	CONTROL (UNTR) 01-0160	CONTROL (VEH) 01-0175	LOW DOSE 01-0165	HIGH DOSE 01-0170
FIBROSIS, FOCAL			1 (2%)	1 (2%)
INFARCT, FOCAL			1 (2%)	
HEMOSIDEROSIS	2 (4%)			
HYPERPLASIA, HEMATOPOIETIC			1 (2%)	
HYPERPLASIA, RETICULUM CELL				1 (2%)
#SPLENIC FOLLICLES	(50)	(25)	(47)	(43)
ATROPHY, NOS				2 (5%)
#MANDIBULAR L. NODE	(49)	(23)	(45)	(40)
HYPERPLASIA, PLASMA CELL	1 (2%)			
#CERVICAL LYMPH NODE	(49)	(23)	(45)	(40)
PIGMENTATION, NOS			1 (2%)	
#PANCREATIC L.NODE	(49)	(23)	(45)	(40)
HEMORRHAGE			1 (2%)	
FIBROSIS			1 (2%)	
HYPERPLASIA, HEMATOPOIETIC			1 (2%)	
#LUMBAR LYMPH NODE	(49)	(23)	(45)	(40)
LYMPHANGIECTASIS			1 (2%)	
#MESENTERIC L. NODE	(49)	(23)	(45)	(40)
ATROPHY, NOS				1 (3%)
HYPERPLASIA, PLASMA CELL	1 (2%)			
#RENAL LYMPH NODE	(49)	(23)	(45)	(40)
HEMORRHAGE				1 (3%)
HYPERPLASIA, HEMATOPOIETIC			1 (2%)	
#THYMUS	(24)	(20)	(40)	(29)
CYST, NOS			2 (5%)	1 (3%)
HEMORRHAGE		1 (5%)		
ATROPHY, NOS			1 (3%)	2 (7%)
CIRCULATORY SYSTEM				
#HEART	(48)	(25)	(47)	(44)
PERIARTERITIS		1 (4%)	1 (2%)	
#HEART/VENTRICLE	(48)	(25)	(47)	(44)
HYPERPLASIA, FOCAL			1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

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TABLE C1 (CONTINUED)

	CONTROL(UNTR) 01-0160	CONTROL(VEH) 01-0175	LOW DOSE 01-0165	HIGH DOSE 01-0170
#MYOCARDIUM	(48)	(25)	(47)	(44)
INFLAMMATION, NOS			1 (2%)	
INFLAMMATION, INTERSTITIAL	1 (2%)			
FIBROSIS	2 (4%)			1 (2%)
DEGENERATION, NOS	1 (2%)			1 (2%)
NECROSIS, FOCAL				1 (2%)
*AORTA	(50)	(25)	(47)	(45)
INFLAMMATION, CHRONIC				1 (2%)
*PULMONARY ARTERY	(50)	(25)	(47)	(45)
MINERALIZATION		11 (44%)	18 (38%)	11 (24%)
*SUBCOSTAL ARTERY	(50)	(25)	(47)	(45)
PERIVASCULITIS				1 (2%)
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(50)	(23)	(46)	(42)
HYPERPLASIA, INTRADUCTAL	1 (2%)			
#LIVER	(49)	(25)	(47)	(45)
CONGESTION, NOS				1 (2%)
INFLAMMATION, CHRONIC FOCAL	1 (2%)			
NECROSIS, FOCAL	3 (6%)			1 (2%)
METAMORPHOSIS FATTY			1 (2%)	
BASOPHILIC CYTO CHANGE		5 (20%)	7 (15%)	6 (13%)
EOSINOPHILIC CYTO CHANGE			4 (9%)	2 (4%)
CLEAR-CELL CHANGE				5 (11%)
HYPERPLASIA, FOCAL	1 (2%)			2 (4%)
#LIVER/CENTRILOBULAR	(49)	(25)	(47)	(45)
CONGESTION, PASSIVE	1 (2%)			
METAMORPHOSIS FATTY				1 (2%)
*BILE DUCT	(50)	(25)	(47)	(45)
HYPERPLASIA, NOS	2 (4%)			
#PANCREAS	(47)	(24)	(45)	(41)
INFLAMMATION, NOS	2 (4%)		1 (2%)	
INFLAMMATION, FOCAL		1 (4%)		1 (2%)
INFLAMMATION, CHRONIC				1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1 (CONTINUED)

	CONTROL (UNTR) 01-0160	CONTROL (VEH) 01-0175	LOW DOSE 01-0165	HIGH DOSE 01-0170
INFLAMMATION, CHRONIC FOCAL	1 (2%)			1 (2%)
PERIARTERITIS			2 (4%)	
#ESOPHAGUS	(48)	(19)	(42)	(40)
NECROSIS, NOS				1 (3%)
#PERIESOPHAGEAL TISSU	(48)	(19)	(42)	(40)
INFLAMMATION, NOS			1 (2%)	
INFLAMMATION, ACUTE FOCAL			1 (2%)	
NECROSIS, NOS			1 (2%)	
#STOMACH	(49)	(25)	(44)	(41)
INFLAMMATION, NOS				1 (2%)
HYPERKERATOSIS	1 (2%)			1 (2%)
ACANTHOSIS	1 (2%)			1 (2%)
#PEYERS PATCH	(49)	(25)	(45)	(43)
HYPERPLASIA, NOS	1 (2%)			
#COLON	(48)	(25)	(45)	(40)
MINERALIZATION				1 (3%)
NEMATODIASIS			3 (7%)	3 (8%)
PARASITISM		2 (8%)	1 (2%)	
URINARY SYSTEM				
#KIDNEY	(50)	(25)	(47)	(45)
HYDRONEPHROSIS			1 (2%)	
CONGESTION, NOS	1 (2%)			
GLOMERULONEPHRITIS, NOS	4 (8%)			
INFLAMMATION, NOS			1 (2%)	
INFLAMMATION, INTERSTITIAL		1 (4%)		
GLOMERULONEPHRITIS, CHRONIC				32 (71%)
FIBROSIS, DIFFUSE				1 (2%)
PERIARTERITIS				1 (2%)
NEPHROPATHY		16 (64%)	41 (87%)	6 (13%)
NEPHROSIS, NOS	35 (70%)			2 (4%)
NECROSIS, MEDULLARY			1 (2%)	3 (7%)
CALCIFICATION, NOS				1 (2%)
HYPERPLASIA, TUBULAR CELL				1 (2%)
#KIDNEY/MEDULLA	(50)	(25)	(47)	(45)
MINERALIZATION			1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1 (CONTINUED)

	CONTROL(UNTR) 01-0160	CONTROL(VEH) 01-0175	LOW DOSE 01-0165	HIGH DOSE 01-0170
#RENAL PAPILLA	(50)	(25)	(47)	(45)
MINERALIZATION			7 (15%)	27 (60%)
HEMORRHAGE				1 (2%)
NECROSIS, FOCAL				1 (2%)
#KIDNEY/PELVIS	(50)	(25)	(47)	(45)
HYPERPLASIA, EPITHELIAL				26 (58%)
#URINARY BLADDER	(50)	(25)	(45)	(44)
INFLAMMATION, ACUTE NECROTIZING			1 (2%)	
ENDOCRINE SYSTEM				
#PITUITARY	(45)	(22)	(45)	(37)
CYST, NOS				1 (3%)
CONGESTION, NOS	1 (2%)			
HEMORRHAGE		1 (5%)	1 (2%)	1 (3%)
HYPERPLASIA, FOCAL			2 (4%)	6 (16%)
HYPERPLASIA, CHROMOPHOBE-CELL		1 (5%)		
#ADRENAL	(50)	(25)	(47)	(45)
HEMORRHAGE			1 (2%)	
METAMORPHOSIS FATTY			1 (2%)	
#ADRENAL CORTEX	(50)	(25)	(47)	(45)
NODULE			1 (2%)	
#ADRENAL MEDULLA	(50)	(25)	(47)	(45)
HYPERPLASIA, NOS				1 (2%)
HYPERPLASIA, FOCAL		1 (4%)	1 (2%)	1 (2%)
#THYROID	(37)	(23)	(44)	(39)
CYST, NOS			1 (2%)	
CYSTIC FOLLICLES	1 (3%)		1 (2%)	
HYPERPLASIA, C-CELL	2 (5%)	6 (26%)	4 (9%)	1 (3%)
METAPLASIA, SQUAMOUS		1 (4%)		
#PARATHYROID	(20)	(12)	(20)	(18)
HYPERPLASIA, NOS				1 (6%)
#PANCREATIC ISLETS	(47)	(24)	(45)	(41)
HYPERPLASIA, NOS				1 (2%)
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(50)	(25)	(47)	(45)
GALACTOCELE			1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1 (CONTINUED)

	CONTROL (UNTR) 01-0160	CONTROL (VEH) 01-0175	LOW DOSE 01-0165	HIGH DOSE 01-0170
#PROSTATE	(48)	(24)	(44)	(43)
MINERALIZATION			1 (2%)	
HEMORRHAGE			1 (2%)	
INFLAMMATION, NOS	3 (6%)		1 (2%)	
INFLAMMATION, FOCAL		1 (4%)		
INFLAMMATION, ACUTE			2 (5%)	1 (2%)
INFLAMMATION, ACUTE FOCAL		5 (21%)	5 (11%)	7 (16%)
INFLAMMATION ACUTE AND CHRONIC			1 (2%)	
METAPLASIA, SQUAMOUS			1 (2%)	
*SEMINAL VESICLE	(50)	(25)	(47)	(45)
HEMORRHAGE			1 (2%)	
INFLAMMATION, ACUTE FOCAL			1 (2%)	
ATROPHY, NOS				1 (2%)
HYPERPLASIA, PAPILLARY			1 (2%)	
#TESTIS	(50)	(25)	(45)	(44)
PERIARTERITIS				1 (2%)
PERIVASCULITIS	1 (2%)			
CALCIFICATION, NOS	3 (6%)			
CALCIFICATION, FOCAL	1 (2%)			
ATROPHY, NOS	11 (22%)			
ATROPHY, FOCAL				1 (2%)
HYPERPLASIA, INTERSTITIAL CELL	4 (8%)	1 (4%)	2 (4%)	
#TESTIS/TUBULE	(50)	(25)	(45)	(44)
MINERALIZATION				1 (2%)
DEGENERATION, NOS				2 (5%)
NERVOUS SYSTEM				
#BRAIN	(50)	(24)	(45)	(42)
INFARCT, FOCAL			1 (2%)	
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
*SKELETAL MUSCLE	(50)	(25)	(47)	(45)
MINERALIZATION				1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1 (CONCLUDED)

	CONTROL (UNTR) 01-0160	CONTROL (VEH) 01-0175	LOW DOSE 01-0165	HIGH DOSE 01-0170
BODY CAVITIES				
*MEDIASTINUM	(50)	(25)	(47)	(45)
INFLAMMATION, ACUTE		1 (4%)		
*PLEURA	(50)	(25)	(47)	(45)
FIBROSIS, DIFFUSE	1 (2%)			
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(50)	(25)	(47)	(45)
MINERALIZATION				1 (2%)
NECK				
INFLAMMATION, FOCAL			1	
ADIPOSE TISSUE				
INFLAMMATION, CHRONIC			1	2
OMENTUM				
NECROSIS, FAT			2	
PIGMENTATION, NOS				1
SPECIAL MORPHOLOGY SUMMARY				
AUTOLYSIS/NO NECROPSY			3	5

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS TREATED WITH m-CRESIDINE

	CONTROL (UNTR) 02-0160	CONTROL (VEH) 02-0175	LOW DOSE 02-0165	HIGH DOSE 02-0170
ANIMALS INITIALLY IN STUDY	50	25	@49	50
ANIMALS MISSING	1			
ANIMALS NECROPSIED	49	24	49	46
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	49	24	49	45
INTEGUMENTARY SYSTEM				
*SKIN	(49)	(24)	(49)	(46)
EPIDERMAL INCLUSION CYST				1 (2%)
ATROPHY, NOS				1 (2%)
RESPIRATORY SYSTEM				
#LUNG/BRONCHUS	(49)	(24)	(49)	(45)
INFLAMMATION, NOS			1 (2%)	
#LUNG	(49)	(24)	(49)	(45)
CONGESTION, NOS		1 (4%)		
CONGESTION, ACUTE PASSIVE	1 (2%)			
EDEMA, NOS			2 (4%)	
HEMORRHAGE			2 (4%)	
INFLAMMATION, FOCAL		1 (4%)		1 (2%)
INFLAMMATION, INTERSTITIAL				1 (2%)
INFLAMMATION, CHRONIC				1 (2%)
PERIARTERITIS		1 (4%)		
CYTOMEGALY				1 (2%)
HYPERPLASIA, ALVEOLAR EPITHELIUM		2 (8%)		
HEMATOPOIETIC SYSTEM				
#BONE MARROW	(45)	(24)	(47)	(44)
HYPERPLASIA, HEMATOPOIETIC				1 (2%)
#SPLEEN	(47)	(24)	(48)	(45)
HEMOSIDEROSIS	3 (6%)			
HYPERPLASIA, HEMATOPOIETIC		1 (4%)		
HEMATOPOIESIS			1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS
@NOTE: 50 ANIMALS WERE INITIALLY IN STUDY BUT ONE WAS FOUND TO BE A MALE IN A FEMALE GROUP AND WAS DELETED.

TABLE C2 (CONTINUED)

	CONTROL (UNTR) 02-0160	CONTROL (VEH) 02-0175	LOW DOSE 02-0165	HIGH DOSE 02-0170
#SPLENIC FOLLICLES	(47)	(24)	(48)	(45)
ATROPHY, NOS			1 (2%)	
#MEDIASTINAL L.NODE	(44)	(24)	(46)	(39)
HEMORRHAGE			1 (2%)	
#MESENTERIC L. NODE	(44)	(24)	(46)	(39)
HEMORRHAGE			1 (2%)	
#THYMUS	(30)	(18)	(38)	(29)
CYST, NOS			1 (3%)	
HEMORRHAGE		1 (6%)		
CIRCULATORY SYSTEM				
#HEART	(48)	(24)	(48)	(45)
NECROSIS, FOCAL				1 (2%)
#MYOCARDIUM	(48)	(24)	(48)	(45)
FIBROSIS	1 (2%)			
DEGENERATION, NOS				1 (2%)
*ARTERY	(49)	(24)	(49)	(46)
NECROSIS, FOCAL				1 (2%)
*PULMONARY ARTERY	(49)	(24)	(49)	(46)
MINERALIZATION		5 (21%)	6 (12%)	1 (2%)
DIGESTIVE SYSTEM				
#LIVER	(48)	(24)	(49)	(44)
INFLAMMATION, ACUTE				1 (2%)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)			
INFLAMMATION, CHRONIC FOCAL	1 (2%)			
NECROSIS, NOS			1 (2%)	
NECROSIS, FOCAL	1 (2%)		1 (2%)	1 (2%)
METAMORPHOSIS FATTY	1 (2%)	2 (8%)	8 (16%)	3 (7%)
BASOPHILIC CYTO CHANGE	2 (4%)	17 (71%)	21 (43%)	2 (5%)
EOSINOPHILIC CYTO CHANGE			4 (8%)	1 (2%)
CLEAR-CELL CHANGE				1 (2%)
HYPERPLASIA, FOCAL	1 (2%)			1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2 (CONTINUED)

	CONTROL (UNTR) 02-0160	CONTROL (VEH) 02-0175	LOW DOSE 02-0165	HIGH DOSE 02-0170
ANGIECTASIS				2 (5%)
HEMATOPOIESIS		1 (4%)		
#LIVER/HEPATOCYTES	(48)	(24)	(49)	(44)
NUCLEAR ALTERATION		1 (4%)		
*BILE DUCT	(49)	(24)	(49)	(46)
HYPERPLASIA, NOS	2 (4%)			
HYPERPLASIA, FOCAL	1 (2%)			
#PANCREAS	(48)	(23)	(46)	(42)
INFLAMMATION, CHRONIC				1 (2%)
INFLAMMATION, CHRONIC FOCAL				1 (2%)
PERIARTERITIS				1 (2%)
NECROSIS, FOCAL				1 (2%)
#PANCREATIC ACINUS	(48)	(23)	(46)	(42)
ATROPHY, FOCAL				1 (2%)
#ESOPHAGUS	(49)	(18)	(41)	(37)
DILATATION, NOS		1 (6%)		
EPIDERMAL INCLUSION CYST				1 (3%)
NECROSIS, NOS				1 (3%)
#STOMACH	(49)	(23)	(45)	(45)
INFLAMMATION, NOS	1 (2%)			
NECROSIS, FOCAL				1 (2%)
#GASTRIC SUBMUCOSA	(49)	(23)	(45)	(45)
EDEMA, NOS	1 (2%)			
#PEYERS PATCH	(49)	(23)	(46)	(45)
HYPERPLASIA, NOS	2 (4%)			
#ILEUM	(49)	(24)	(46)	(45)
ULCER, FOCAL			1 (2%)	
#COLON	(49)	(24)	(46)	(44)
NEMATODIASIS			2 (4%)	2 (5%)
PARASITISM	1 (2%)	3 (13%)	3 (7%)	
URINARY SYSTEM				
#KIDNEY	(48)	(24)	(49)	(45)
MINERALIZATION			5 (10%)	1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2 (CONTINUED)

	CONTROL(UNTR) 02-0160	CONTROL(VEH) 02-0175	LOW DOSE 02-0165	HIGH DOSE 02-0170
CYST, NOS			1 (2%)	
GLOMERULONEPHRITIS, NOS	4 (8%)			
GLOMERULONEPHRITIS, CHRONIC				26 (58%)
NEPHROPATHY		17 (71%)	37 (76%)	11 (24%)
NEPHROSIS, NOS	29 (60%)			
NECROSIS, FOCAL				1 (2%)
POSTMORTEM CHANGE			1 (2%)	
NECROSIS, MEDULLARY				4 (9%)
#KIDNEY/CORTEX	(48)	(24)	(49)	(45)
METAMORPHOSIS FATTY	1 (2%)			
#KIDNEY/MEDULLA	(48)	(24)	(49)	(45)
CALCIFICATION, NOS				1 (2%)
#RENAL PAPILLA	(48)	(24)	(49)	(45)
MINERALIZATION			3 (6%)	34 (76%)
INFLAMMATION, ACUTE FOCAL				1 (2%)
NECROSIS, NOS				2 (4%)
#KIDNEY/PELVIS	(48)	(24)	(49)	(45)
MINERALIZATION			4 (8%)	
HYPERPLASIA, EPITHELIAL				29 (64%)
ENDOCRINE SYSTEM				
#PITUITARY	(39)	(23)	(42)	(36)
CYST, NOS			1 (2%)	
HYPERPLASIA, FOCAL			1 (2%)	
HYPERPLASIA, CHROMOPHOBE-CELL			1 (2%)	
#ADRENAL	(49)	(24)	(47)	(45)
ANGIECTASIS			1 (2%)	
#ADRENAL CORTEX	(49)	(24)	(47)	(45)
HYPERPLASIA, NODULAR				1 (2%)
#ADRENAL MEDULLA	(49)	(24)	(47)	(45)
HYPERPLASIA, NOS			1 (2%)	
#THYROID	(45)	(23)	(45)	(41)
CYST, NOS			1 (2%)	
COLLOID CYST				1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2 (CONTINUED)

	CONTROL (UNTR) 02-0160	CONTROL (VEH) 02-0175	LOW DOSE 02-0165	HIGH DOSE 02-0170
HYPERPLASIA, PAPILLARY				1 (2%)
HYPERPLASIA, C-CELL	2 (4%)	2 (9%)		
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(49)	(24)	(49)	(46)
DILATATION/DUCTS	1 (2%)			
GALACTOCELE		3 (13%)	15 (31%)	3 (7%)
HYPERPLASIA, NOS			1 (2%)	
HYPERPLASIA, FOCAL		1 (4%)		
*MAMMARY DUCT	(49)	(24)	(49)	(46)
HYPERPLASIA, CYSTIC	1 (2%)			
*MAMMARY LOBULE	(49)	(24)	(49)	(46)
HYPERPLASIA, NOS		1 (4%)	4 (8%)	
*CLITORAL GLAND	(49)	(24)	(49)	(46)
INFLAMMATION, FOCAL GRANULOMATOU		1 (4%)		
#UTERUS	(46)	(24)	(47)	(44)
HYDROMETRA	1 (2%)		2 (4%)	2 (5%)
HEMATOMA, NOS	1 (2%)			
POLYP, INFLAMMATORY	1 (2%)			
#UTERUS/ENDOMETRIUM	(46)	(24)	(47)	(44)
HYPERPLASIA, CYSTIC			3 (6%)	1 (2%)
#OVARY	(47)	(24)	(45)	(45)
INFLAMMATION, CHRONIC	1 (2%)			
NERVOUS SYSTEM				
#BRAIN	(49)	(24)	(47)	(43)
HEMORRHAGE			1 (2%)	
SPECIAL SENSE ORGANS				
*EYE	(49)	(24)	(49)	(46)
INFLAMMATION, CHRONIC				1 (2%)
CATARACT				1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2 (CONTINUED)

	CONTROL (UNTR) 02-0160	CONTROL (VEH) 02-0175	LOW DOSE 02-0165	HIGH DOSE 02-0170
*EYE/CORNEA	(49)	(24)	(49)	(46)
INFLAMMATION PROLIFERATIVE			1 (2%)	
*LENS CAPSULE	(49)	(24)	(49)	(46)
CALCIFICATION, NOS	1 (2%)			
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*MEDIASTINUM	(49)	(24)	(49)	(46)
EDEMA, NOS			1 (2%)	
PERIARTERITIS				2 (4%)
*MESENTERY	(49)	(24)	(49)	(46)
PERIARTERITIS			1 (2%)	
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(49)	(24)	(49)	(46)
NECROSIS, FOCAL				1 (2%)
ADIPOSE TISSUE				
INFLAMMATION, CHRONIC				2
OMENTUM				
INFLAMMATION, NOS		1		
NECROSIS, NOS			1	
NECROSIS, FAT		1		
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED	2	1	1	2
ANIMAL MISSING/NO NECROPSY	1			
AUTO/NECROPSY/HISTO PERF			2	
AUTO/NECROPSY/NO HISTO				1

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2 (CONCLUDED)

	CONTROL(UNTR) 02-0160	CONTROL(VEH) 02-0175	LOW DOSE 02-0165	HIGH DOSE 02-0170
AUTOLYSIS/NO NECROPSY		1		4

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE TREATED WITH m-CRESIDINE

TABLE D1
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE TREATED WITH m-CRESIDINE

	CONTROL (UNTR) 05-0160	CONTROL (VEH) 05-0175	LOW DOSE 05-0165	HIGH DOSE 05-0170
ANIMALS INITIALLY IN STUDY	50	25	50	50
ANIMALS MISSING				1
ANIMALS NECROPSIED	50	24	46	41
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	49	24	45	36
INTEGUMENTARY SYSTEM				
*SUBCUT TISSUE	(50)	(24)	(46)	(41)
HEMATOMA, NOS	1 (2%)			
INFLAMMATION, ACUTE FOCAL	1 (2%)			
ABSCESS, NOS	1 (2%)			
RESPIRATORY SYSTEM				
NONE				
HEMATOPOIETIC SYSTEM				
#BONE MARROW	(49)	(21)	(41)	(33)
HYPERPLASIA, HEMATOPOIETIC			1 (2%)	
#SPLEEN	(49)	(24)	(41)	(32)
ATROPHY, NOS			14 (34%)	18 (56%)
HEMATOPOIESIS		1 (4%)		
ERYTHROPOIESIS	2 (4%)			
#MANDIBULAR L. NODE	(40)	(20)	(31)	(26)
ATROPHY, NOS				1 (4%)
#MESENTERIC L. NODE	(40)	(20)	(31)	(26)
HEMORRHAGE		10 (50%)	2 (6%)	1 (4%)
ATROPHY, NOS				2 (8%)
#RENAL LYMPH NODE	(40)	(20)	(31)	(26)
HYPERPLASIA, NOS	2 (5%)			
#THYMUS	(30)	(16)	(24)	(19)
ATROPHY, NOS			16 (67%)	15 (79%)

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE D1 (CONTINUED)

	CONTROL(UNTR) 05-0160	CONTROL(VEH) 05-0175	LOW DOSE 05-0165	HIGH DOSE 05-0170
CIRCULATORY SYSTEM				
#HEART	(49)	(24)	(44)	(36)
THROMBOSIS, NOS			1 (2%)	
INFLAMMATION, CHRONIC		1 (4%)		
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(47)	(23)	(43)	(34)
LYMPHOCYTIC INFLAMMATORY INFILTR		17 (74%)	4 (9%)	
#LIVER	(49)	(24)	(44)	(36)
NECROSIS, FOCAL				1 (3%)
METAMORPHOSIS FATTY	1 (2%)			
CYTOPLASMIC VACUOLIZATION		1 (4%)	1 (2%)	3 (8%)
BASOPHILIC CYTO CHANGE		2 (8%)		
ANGIECTASIS	1 (2%)			
#LIVER/KUPFFER CELL	(49)	(24)	(44)	(36)
HYPERPLASIA, NOS	1 (2%)			
#LIVER/HEPATOCYTES	(49)	(24)	(44)	(36)
CYTOPLASMIC VACUOLIZATION			10 (23%)	11 (31%)
#PANCREAS	(46)	(22)	(37)	(32)
CYSTIC DUCTS	1 (2%)			
PERIVASCULITIS	1 (2%)			
NECROSIS, FAT	1 (2%)			
ATROPHY, FATTY		2 (9%)		
#STOMACH	(49)	(24)	(39)	(35)
ULCER, NOS				3 (9%)
INFLAMMATION, ACUTE FOCAL		1 (4%)		
CALCIFICATION, FOCAL			1 (3%)	2 (6%)
HYPERPLASIA, FOCAL				1 (3%)
#PEYERS PATCH	(49)	(24)	(37)	(35)
INFLAMMATION, ACUTE	1 (2%)			
HYPERPLASIA, LYMPHOID	1 (2%)			
#COLON	(48)	(20)	(32)	(30)
PARASITISM		2 (10%)	3 (9%)	3 (10%)
URINARY SYSTEM				
#KIDNEY	(49)	(24)	(43)	(36)
HYDRONEPHROSIS	2 (4%)			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D1 (CONTINUED)

	CONTROL (UNTR) 05-0160	CONTROL (VEH) 05-0175	LOW DOSE 05-0165	HIGH DOSE 05-0170
PYELONEPHRITIS, NOS			2 (5%)	
INFLAMMATION, CHRONIC	1 (2%)			
NEPHROSIS, NOS		1 (4%)	28 (65%)	32 (89%)
#RENAL PAPILLA	(49)	(24)	(43)	(36)
NECROSIS, NOS			13 (30%)	20 (56%)
ENDOCRINE SYSTEM				
#THYROID	(42)	(22)	(34)	(23)
HYPERPLASIA, FOCAL	1 (2%)			
HYPERPLASIA, FOLLICULAR-CELL		1 (5%)		
#PARATHYROID	(20)	(14)	(20)	(14)
HYPERPLASIA, NOS		1 (7%)		
#PANCREATIC ISLETS	(46)	(22)	(37)	(32)
HYPERPLASIA, NOS		3 (14%)		
REPRODUCTIVE SYSTEM				
*PREPUTIAL GLAND	(50)	(24)	(46)	(41)
DILATATION, NOS	1 (2%)		1 (2%)	
#TESTIS	(49)	(24)	(41)	(35)
DEGENERATION, NOS			1 (2%)	
CALCIFICATION, FOCAL			1 (2%)	3 (9%)
MULTINUCLEATE GIANT-CELL			10 (24%)	22 (63%)
ATROPHY, NOS			3 (7%)	2 (6%)
ATROPHY, FOCAL		5 (21%)		
HYPERPLASIA, INTERSTITIAL CELL			1 (2%)	
#TESTIS/TUBULE	(49)	(24)	(41)	(35)
NECROSIS, FOCAL	1 (2%)			
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
NONE				

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D1 (CONCLUDED)

	CONTROL (UNTR) 05-0160	CONTROL (VEH) 05-0175	LOW DOSE 05-0165	HIGH DOSE 05-0170
BODY CAVITIES				
*ABDOMINAL CAVITY	(50)	(24)	(46)	(41)
ADHESION, NOS	1 (2%)			
*MESENTERY	(50)	(24)	(46)	(41)
STEATITIS	1 (2%)			
ABSCESS, NOS	1 (2%)			
ALL OTHER SYSTEMS				
ADIPOSE TISSUE				
STEATITIS	1			
NECROSIS, FAT	2			
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED	17	2	2	
ANIMAL MISSING/NO NECROPSY				1
ACCIDENTAL DEATH				1
AUTO/NECROPSY/HISTO PERF	1		1	
AUTO/NECROPSY/NO HISTO	1		1	5
AUTOLYSIS/NO NECROPSY		1	4	7

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D2
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE TREATED WITH m-CRESIDINE

	CONTROL (UNTR) 06-0160	CONTROL (VEH) 06-0175	LOW DOSE 06-0165	HIGH DOSE 06-0170
ANIMALS INITIALLY IN STUDY	50	25	50	50
ANIMALS MISSING				2
ANIMALS NECROPSIED	50	24	50	46
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	50	24	50	46
INTEGUMENTARY SYSTEM				
NONE				
RESPIRATORY SYSTEM				
NONE				
HEMATOPOIETIC SYSTEM				
#BONE MARROW	(49)	(22)	(49)	(44)
MYELOFIBROSIS		11 (50%)	17 (35%)	19 (43%)
#SPLEEN	(49)	(23)	(49)	(43)
ATROPHY, NOS				4 (9%)
HYPERPLASIA, LYMPHOID	1 (2%)			
HEMATOPOIESIS		1 (4%)	1 (2%)	
ERYTHROPOIESIS	1 (2%)			
#MANDIBULAR L. NODE	(40)	(18)	(41)	(40)
HYPERPLASIA, NOS			1 (2%)	
HYPERPLASIA, PLASMA CELL	1 (3%)			
#MEDIASTINAL L.NODE	(40)	(18)	(41)	(40)
HYPERPLASIA, NOS	1 (3%)			
#LUMBAR LYMPH NODE	(40)	(18)	(41)	(40)
HYPERPLASIA, NOS	1 (3%)			
#MESENTERIC L. NODE	(40)	(18)	(41)	(40)
HEMORRHAGE		5 (28%)	1 (2%)	2 (5%)
ATROPHY, NOS				1 (3%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE D2 (CONTINUED)

	CONTROL (UNTR) 06-0160	CONTROL (VEH) 06-0175	LOW DOSE 06-0165	HIGH DOSE 06-0170
#RENAL LYMPH NODE	(40)	(18)	(41)	(40)
HYPERPLASIA, NOS	1 (3%)			
HYPERPLASIA, PLASMA CELL	1 (3%)			
#THYMUS	(31)	(15)	(33)	(29)
ATROPHY, NOS				7 (24%)
CIRCULATORY SYSTEM				
#MYOCARDIUM	(50)	(23)	(49)	(44)
INFLAMMATION, ACUTE DIFFUSE	1 (2%)			
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(48)	(23)	(49)	(45)
LYMPHOCYTIC INFLAMMATORY INFILTR		8 (35%)	20 (41%)	18 (40%)
ATROPHY, NOS		1 (4%)		
#LIVER	(49)	(23)	(50)	(45)
NECROSIS, NOS	1 (2%)			1 (2%)
NECROSIS, FOCAL	1 (2%)	1 (4%)	1 (2%)	1 (2%)
INFARCT, NOS	1 (2%)			
HEMATOPOIESIS			1 (2%)	
*BILE DUCT	(50)	(24)	(50)	(46)
INFLAMMATION, CHRONIC FOCAL	2 (4%)			
#PANCREAS	(47)	(23)	(43)	(40)
DILATATION/DUCTS			2 (5%)	
NECROSIS, FAT		1 (4%)		
METAMORPHOSIS FATTY			1 (2%)	
ATROPHY, FATTY		1 (4%)		
#STOMACH	(49)	(23)	(47)	(43)
INFLAMMATION, ACUTE FOCAL	1 (2%)			
INFLAMMATION, CHRONIC	1 (2%)			
#PEYERS PATCH	(49)	(24)	(47)	(42)
HYPERPLASIA, LYMPHOID	1 (2%)			
#COLON	(50)	(23)	(44)	(37)
NEMATODIASIS	1 (2%)			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D2 (CONTINUED)

	CONTROL(UNTR) 06-0160	CONTROL(VEH) 06-0175	LOW DOSE 06-0165	HIGH DOSE 06-0170
PARASITISM				4 (11%)
URINARY SYSTEM				
#KIDNEY	(49)	(23)	(49)	(46)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)			
INFLAMMATION, CHRONIC	2 (4%)			
INFLAMMATION, CHRONIC FOCAL	1 (2%)			
NEPHROSIS, NOS			1 (2%)	17 (37%)
GLOMERULOSCLEROSIS, NOS	1 (2%)	1 (4%)		
PIGMENTATION, NOS			1 (2%)	
CYTOPLASMIC VACUOLIZATION				1 (2%)
#RENAL PAPILLA	(49)	(23)	(49)	(46)
NECROSIS, NOS				6 (13%)
#URINARY BLADDER	(50)	(20)	(49)	(41)
INFLAMMATION, CHRONIC FOCAL	1 (2%)			
#U.BLADDER/SUBMUCOSA	(50)	(20)	(49)	(41)
INFLAMMATION, CHRONIC	1 (2%)			
INFLAMMATION, CHRONIC FOCAL	16 (32%)			
PERIVASCULITIS	1 (2%)			
#U.BLADDER/MUSCULARIS	(50)	(20)	(49)	(41)
CALCIUM DEPOSIT	1 (2%)			
ENDOCRINE SYSTEM				
#THYROID	(41)	(17)	(36)	(32)
HYPERPLASIA, C-CELL	2 (5%)			
HYPERPLASIA, FOLLICULAR-CELL	1 (2%)		1 (3%)	
#PANCREATIC ISLETS	(47)	(23)	(43)	(40)
HYPERPLASIA, NOS			1 (2%)	
REPRODUCTIVE SYSTEM				
#UTERUS	(49)	(22)	(46)	(42)
HYDROMETRA	5 (10%)	1 (5%)	1 (2%)	2 (5%)
INFLAMMATION, SUPPURATIVE		1 (5%)		

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D2 (CONTINUED)

	CONTROL (UNTR) 06-0160	CONTROL (VEH) 06-0175	LOW DOSE 06-0165	HIGH DOSE 06-0170
PYOMETRA		2 (9%)		1 (2%)
INFLAMMATION, GRANULOMATOUS				1 (2%)
INFLAMMATION, PYOGRANULOMATOUS		1 (5%)		
NECROSIS, FAT	1 (2%)			
CALCIFICATION, NOS	1 (2%)			
#UTERUS/ENDOMETRIUM	(49)	(22)	(46)	(42)
INFLAMMATION, SUPPURATIVE	2 (4%)			
HYPERPLASIA, NOS			1 (2%)	
HYPERPLASIA, CYSTIC	32 (65%)	10 (45%)	19 (41%)	20 (48%)
#OVARY	(48)	(20)	(39)	(41)
CYST, NOS	6 (13%)			
FOLLICULAR CYST, NOS		1 (5%)		1 (2%)
PAROVARIAN CYST			2 (5%)	3 (7%)
THROMBOSIS, NOS			1 (3%)	
HEMORRHAGIC CYST				1 (2%)
INFLAMMATION, SUPPURATIVE	1 (2%)			
INFLAMMATION, CHRONIC	1 (2%)	1 (5%)	2 (5%)	
INFLAMMATION, GRANULOMATOUS				1 (2%)
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(50)	(24)	(50)	(46)
AMYLOIDOSIS	1 (2%)			

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D2 (CONCLUDED)

	CONTROL(UNTR) 06-0160	CONTROL(VEH) 06-0175	LOW DOSE 06-0165	HIGH DOSE 06-0170
OMENTUM				
PERIVASCULITIS	1			
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED	2	3	9	1
ANIMAL MISSING/NO NECROPSY				2
AUTO/NECROPSY/HISTO PERF	2	1	2	1
AUTOLYSIS/NO NECROPSY		1		2

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

Review of the Bioassay of m-Cresidine* for Carcinogenicity by the Data Evaluation/Risk Assessment Subgroup of the Clearinghouse on Environmental Carcinogens

March 6, 1978

The Clearinghouse on Environmental Carcinogens was established in May, 1976, in compliance with DHEW Committee Regulations and the Provisions of the Federal Advisory Committee Act. The purpose of the Clearinghouse is to advise the Director of the National Cancer Institute (NCI) on its bioassay program to identify and to evaluate chemical carcinogens in the environment to which humans may be exposed. The members of the Clearinghouse have been drawn from academia, industry, organized labor, public interest groups, State health officials, and quasi-public health and research organizations. Members have been selected on the basis of their experience in carcinogenesis or related fields and, collectively, provide expertise in chemistry, biochemistry, biostatistics, toxicology, pathology, and epidemiology. Representatives of various Governmental agencies participate as ad hoc members. The Data Evaluation/Risk Assessment Subgroup of the Clearinghouse is charged with the responsibility of providing a peer review of reports prepared on NCI-sponsored bioassays of chemicals studied for carcinogenicity. It is in this context that the below critique is given on the bioassay of m-Cresidine for carcinogenicity.

The primary reviewer noted that the compound may be of little commercial importance since the quantities produced in the United States were reported to be less than 1,000 pounds or $1,000 in value. He said that m-Cresidine induced papillary transitional-cell carcinomas of the urinary bladder in both sexes of treated rats. It also appeared to cause a dose-related increase in liver tumors in female rats, although it may not be statistically significant when compared to historical controls. The high mortality among the treated male mice precluded an assessment of carcinogenicity in this group. The primary reviewer briefly described the experimental design under which m-Cresidine was tested. Despite the studies' shortcomings, he said that they did not invalidate the conclusion on the carcinogenicity of m-Cresidine. He suggested that the conclusion, with respect to the treated female mice, be reworded to note the dose-related increase in liver tumors with an appropriate qualification indicating that it may not be statistically significant.

The secondary reviewer agreed with the conclusion given in the report. He noted that a mineralization was observed in the urinary bladder of some treated rats. He questioned whether the material may have been involved in the induction of the bladder cancers. A Program pathologist said that the material was likely calcification in the tissue.

It was moved that the report on the bioassay of m-Cresidine be accepted. The motion was seconded and approved unanimously.

Members present were:

Gerald N. Wogan (Chairman), Massachusetts Institute of Technology
Arnold Brown, Mayo Clinic
Lawrence Garfinkel, American Cancer Society
E. Cuyler Hammond, American Cancer Society
Joseph Highland, Environmental Defense Fund
Henry Pitot, University of Wisconsin Medical Center
George Roush, Jr., Monsanto Company
Sheldon Samuels, Industrial Union Department, AFL-CIO
Michael Shimkin, University of California at San Diego
John Weisburger, American Health Foundation
Sidney Wolfe, Health Research Group

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* Subsequent to this review, changes may have been made in the bioassay report either as a result of the review or other reasons. Thus, certain comments and criticisms reflected in the review may no longer be appropriate.

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